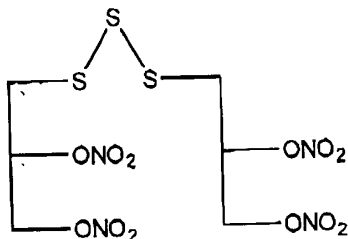40.   A method of mitigating anxiety in a subject in need thereof, comprising administering to a subject an effective amount of a therapeutic compound having the formula IVr:

$$
\begin{array}{c}
S \\
\diagup \diagdown \\
S \qquad S \\
\end{array}
$$

- ONO_2 - ONO_2

- ONO_2 - ONO_2

REMARKS

Claims

Claims 11 to 20, 22, 24, 26, 28, and 33 to 40 are in the case. Claims 12, 15, and 26 have been withdrawn from consideration. Claims 13, 19, and 20 have been amended as described below and shown on the attached sheets entitled "Version With Markings to Show Changes Made". In particular, claims 19 and 20 have been amended to correct typographical errors. Support for the amendments to claims 19 and 20 can be found in, for example, claim 13 as filed. Claims 33 to 40 are drawn to preferred embodiments. Support for new claims 33 to 40 can be found in the specification at, for example:

Claims 33, 34, 35:   pages 22 to 29;

Claim 36:   pages 29 to 33;

Claim 37:   page 31, Example 30 on pages 67 to 68;

Claims 38 to 40:   pages 32 to 38

No new matter has been entered.

Claim Objections

Claim 13 was objected to because of informalities. Applicants submit that claim 13 as amended herein meets the formalities noted by the Examiner.

Rejections Under 35 USC § 112

Claims 13, 14, 16 to 20, 22, 24, 26, and 28 were rejected under 35 USC § 112, second paragraph. The Examiner alleged that claim 13 was indefinite. Applicants submit that claim 13 as amended herein is in compliance with 35 USC § 112, second paragraph.

Rejection Under 35 USC § 102

Claims 11, 13, 14 to 20, 22, 24, and 28 were rejected under 35 USC § 102(a) as anticipated by USPN 5,807,847 (Thatcher *et al.*). The Examiner was of the opinion that the '847 patent teaches a method of effecting tissue relaxation, the method comprising administering an effective amount of a pharmaceutical composition containing an aliphatic nitrate ester corresponding to Applicants' species of Formula Va. Applicants respectfully traverse this rejection for the following reasons:

The Examiner has correctly noted that the '847 patent teaches methods for effecting tissue relaxation. However, the instant claims recite "a method for providing sedation, mitigating anxiety or providing anaesthesia", which is not the same as a method for effecting tissue relaxation. On this basis alone, the '847 patent does not anticipate the instant claims.

The teaching of the '847 patent leaves no doubt as to the non-equivalence of effecting tissue relaxation versus providing sedation or anaesthesia or mitigating anxiety. For instance, the '847 patent teaches that the tissue relaxation response can be elicited in excised rat aortic tissue *in vitro* (see, for example, column 7, lines 18 to 33). The '847 patent thus clearly demonstrates that tissue relaxation is purely a peripheral response which does not invoke or require any central nervous system (CNS) input.

In contrast, the conditions/states recited in the rejected claims, namely, sedation, anxiety, and anaesthesia, all have a behavioural component and hence require CNS function. For example, sedation is defined as "behavioral changes" that include "a supression of responsiveness to a constant level of stimulation, with decreased spontaneous activity and ideation" (see page 371 of Trevor, A.J., *et al.*, Chapter 22. Sedative-Hypnotic Drugs. *In*: Basic & Clinical Pharmacology, 8th Ed., Katzung, B.G., ed., McGraw-Hill, New York, 2001, pp. 364-381; copy enclosed), anxiety is characterized by psychologic, behavioural, and physiologic responses (see page 375 of Trevor *et al.*, *supra*), and anaesthesia is described as a state of pharmacologically-induced depression of the CNS (see page 372 of Trevor *et al.*, *supra*). Thus, sedation, anxiety, and anaesthesia involve fundamentally different physiological processes than tissue relaxation. The '847 patent does not teach or even suggest that a compound useful for effecting tissue relaxation might also be efficacious in a condition/state involving the CNS, such as anxiety, sedation, or anaesthesia. Accordingly, the '847 patent does not anticipate the instant claims.

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In light of the above, withdrawal of the rejection under 35 USC § 102(a) and reconsideration are respectfully requested.

Rejection Under 35 USC § 103

Claims 11, 13, 14 to 20, 22, 24, and 28 were rejected under 35 USC § 103(a) as obvious over by USPN 5,883,122 (Thatcher *et al.*). It was the Examiner's position that it would be obvious that the compound of Formula 1 at col. 11, lines 19 to 20; col. 12, lines 18 to 52 of the '122 patent sedates or mitigates anxiety because pain and anxiety are often associated with myocardial infarctions, dementia, trauma, or withdrawal symptoms. Therefore, according to the Examiner, any anxiety or pain accompanying myocardial infarctions, dementia, trauma, or withdrawal symptoms would effectively be treated when treating such conditions. Applicants respectfully traverse the rejection for the following reasons.

Firstly, the '122 patent does not teach the treatment of pain and/or anxiety. Rather, the '122 patent specifically teaches use of nitrate esters as neuroprotective agents (see for example, col. 1, lines 15 to 18; col. 2, lines 19 to 22; col. 12, lines 10 to 20, lines 25 to 30), *not* as anaesthetic, anxiolytic, or sedative agents. Therefore, the '122 patent provides no teaching or suggestion that the compounds described therein as neuroprotective agents would effectively also treat pain or anxiety.

Secondly, the '122 patent teaches that certain nitrate esters "improve memory performance and cognition" (see for example, col. 11, line 17). In light of this teaching one cannot reasonably expect that a nitrate ester of Formula 1 would provide any anaesthetic, anxiolytic, or sedative efficacy.
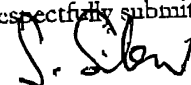
Thirdly, pain that might be associated with conditions such as trauma to the head, dementias, myocardial infarction, epilepsy, or alcohol withdrawal is pain for which *analgesia* is indicated. Analgesia (i.e., pain management) is provided by administration of "pain killers", such ASA or NSAIDs. In contrast, the instant claims recite *anaesthesia*. Analgesia and anaesthesia are distinctly different. For example, Stedman's Medical Dictionary (26th Ed.) defines analgesia as "a neurologic or pharmacologic state in which painful stimuli are so moderated that, though still perceived, they are no longer painful", whereas anaesthesia is defined as "loss of sensation resulting from pharmacological depression of nerve function or from neurological dysfunction" (see also page 372 of Trevor *et al., supra*). Clearly, one would not seek to provide anaesthesia to an individual for whom analgesia (i.e., pain management) is indicated.

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In view of the above, Applicants respectfully submit that only through impermissible hindsight, gained from reading the instant application, could the instant invention be deemed obvious in view of the '122 patent. Accordingly, withdrawal of the rejection under 35 USC § 103(a) and reconsideration are respectfully requested.

If the Examiner has any questions about the instant Response or the application, she is asked to please telephone Stephen Scribner (Reg. No. 44,452) or Carol Miernicki Steeg (Reg. No. 39,539) at 613-533-2342.

Please charge any fees that may be required, for which no cheque is enclosed, to Deposit Account No. 17-0110.

Respectfully submitted,

Stephen J. Scribner
Reg. No. 44, 452

Date: 5 Nov- 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 13, 19, and 20 have been amended as follows:

13.   A method for providing sedation, mitigating anxiety or providing anaesthesia in a subject in need thereof, comprising administering to a subject an effective amount of a therapeutic compound, wherein the therapeutic compound is of the formula (Ic):

$$
\begin{array}{c}
G_2 \\
| \\
G_1 \\
| \\
F_1 \!\!-\!\! C \!\!-\!\! F_2 \\
| \\
E \!\!-\!\! ONO_2
\end{array}
$$

(Ic)
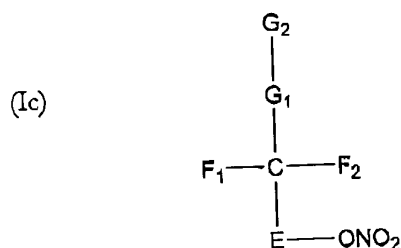
in which E is $(R^1R^2C)_m$ and $G_2\!-\!G_1\!-\!CF_1F_2\!-$ is $R^{19}\!-\!(R^3R^4C)_p\!-\!(R^{17}R^{18}C)_n\!-$;

    wherein: m, n, p are integers from 0 to 10;

            $R^{3,17}$ are each independently hydrogen, a nitrate group, or A; and

            $R^{1,4}$ are each independently hydrogen, or A;

    where A is selected from a substituted or unsubstituted aliphatic group ([preferably] comprising a branched or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally may contain O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally may contain O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally may contain O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group ([preferably] comprising a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain) containing carbonyl linkages ([e.g.,] selected from C=O, C=S, and C=NOH), which optionally may contain O, S, NR^6 and unsaturations in the chain, optionally

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bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; an amino group ([including] selected from alkylamino, dialkylamino, [(including)]cyclic amino, diamino and triamino moieties[)], arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

wherein X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A or X-Y;

R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives which may contain 1-4 ONO_2 substituents; or are each independently hydrogen, a nitrate group or A;

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3; or other pharmaceutically acceptable counterion;

and with the proviso that when m = n = p = 1 and R^{19}, R^2, R^{18}, R^1 = H and R^{17}, R^3 are nitrate groups, R^4 is not H.

19. The method of claim 18, wherein:

X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, or [SSR^4] SSR^5; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, or SSR^5, or does not exist.
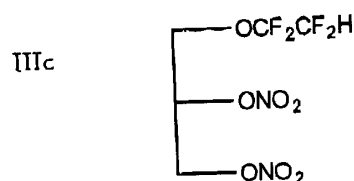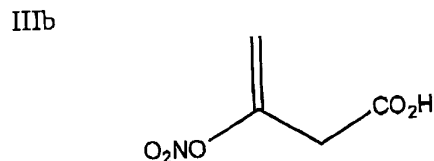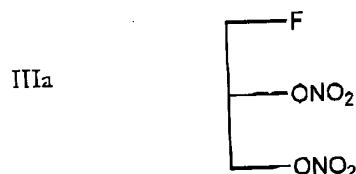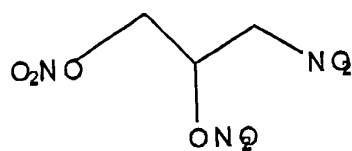
20.   The method of claim 18, wherein:

R^5, R^6, R^8, R^9, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different and are alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, PO_3HM or $P(O)(OM)R^{15}$; and

Y is SO_2M, SO_3M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, SR^5, [SR^4] $\underline{SR^7}$ or SSR^5, or does not exist.

Claims 33 to 40 have been entered as follows:

--33.   A method of providing sedation or mitigating anxiety in a subject in need thereof, comprising administering to a subject an effective amount of a therapeutic compound selected from the group consisting of:

IIIa

IIIb

IIIc

IIId

O_2NO ... NO_2

ONO_2

IIIe

O_2NO ...

IIIf

O_2NO ...

ONO_2

IIIg

IIIh

O_2NO — $S-S$ — ... ONO_2 / ONO_2 / ONO_2 / ONO_2 / ONO_2

IIIi

IIIj

- Br
- ONO_2
- ONO_2
- Br

IIIk

- SCN
- ONO_2
- ONO_2
- SCN

IIIl

- Br
- ONO_2
- ONO_2
- SCN

IIIm

28

IIIn

IIIo

$$CH_2Br-CH(ONO_2)-CH(OH)-CH_2Br$$

,
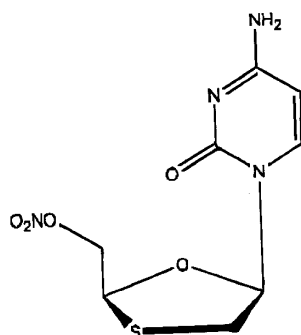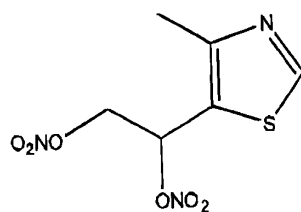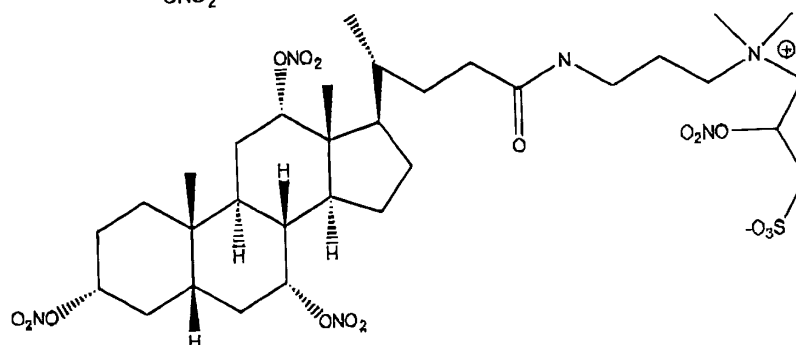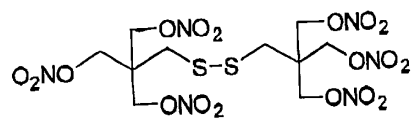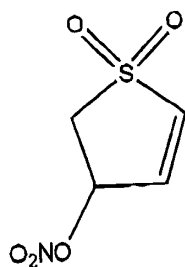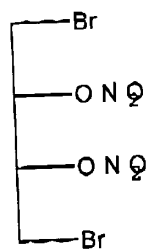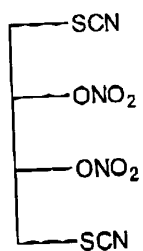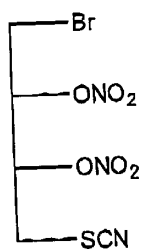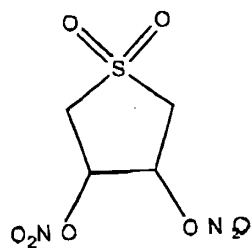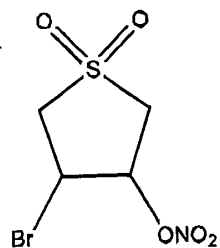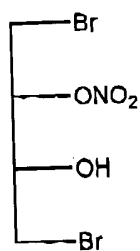
IIIp

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IIIr

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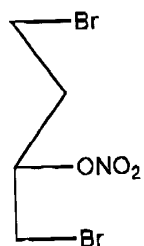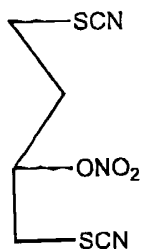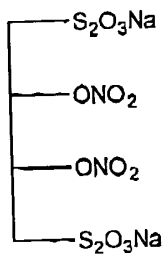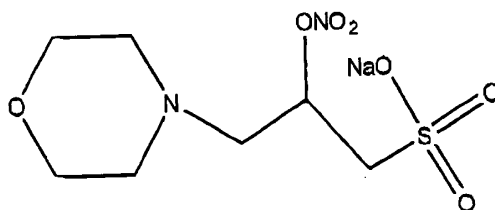
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IIIaa

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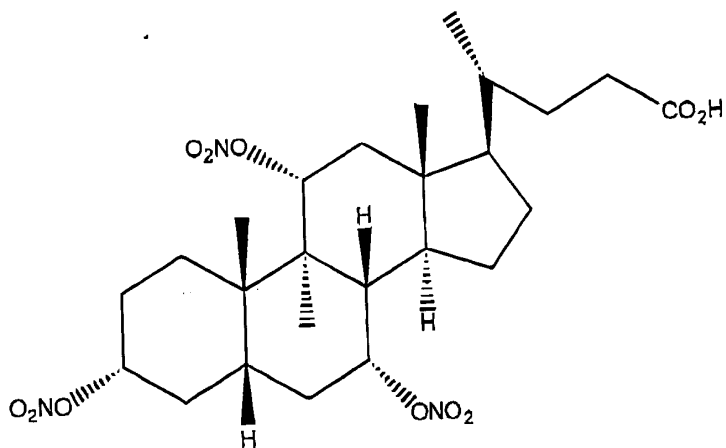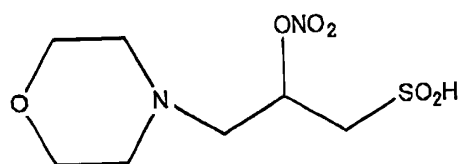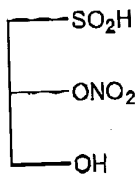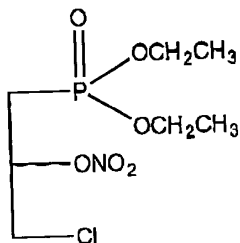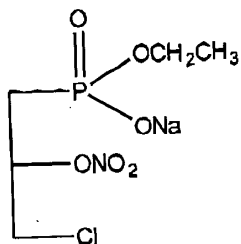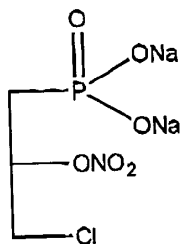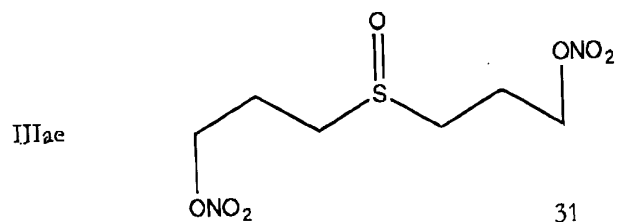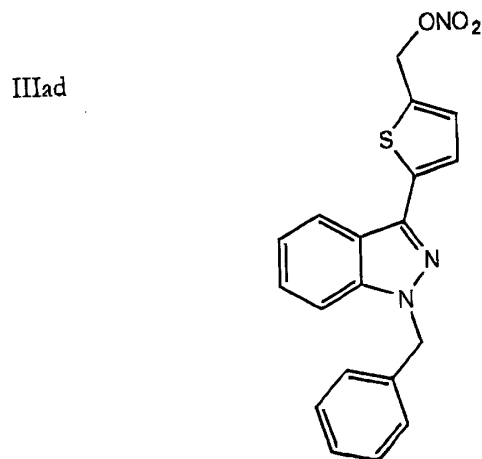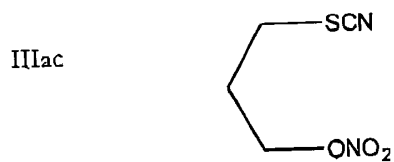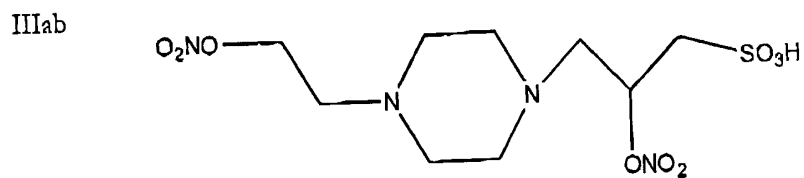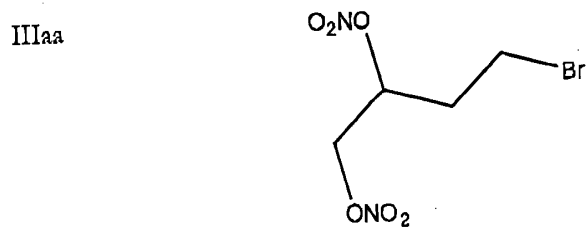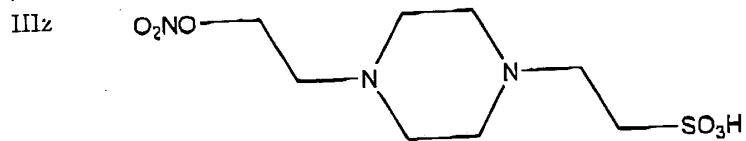
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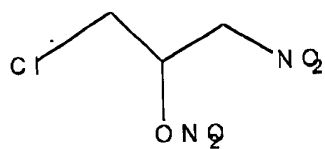
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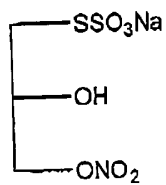
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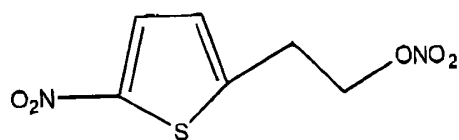
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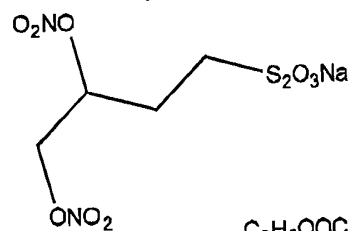
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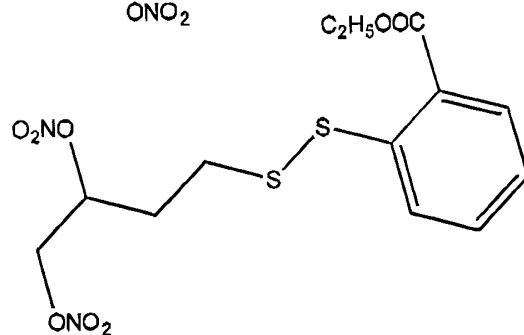
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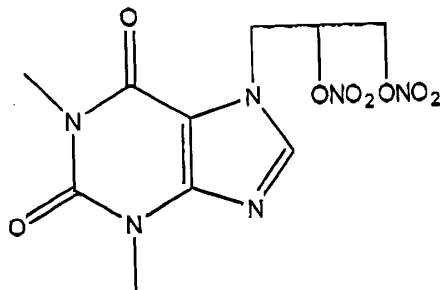
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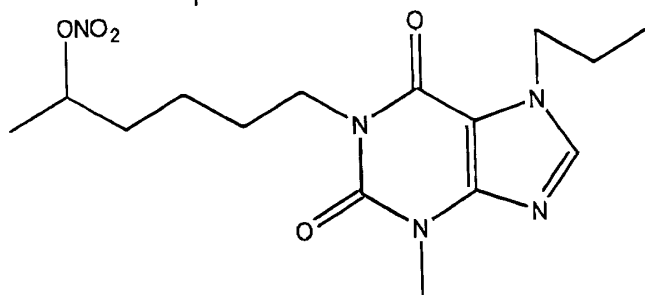
, and

IIIam
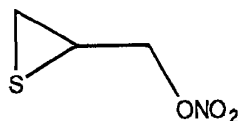
34.   The method of claim 33, wherein the compound has the formula IIIt:
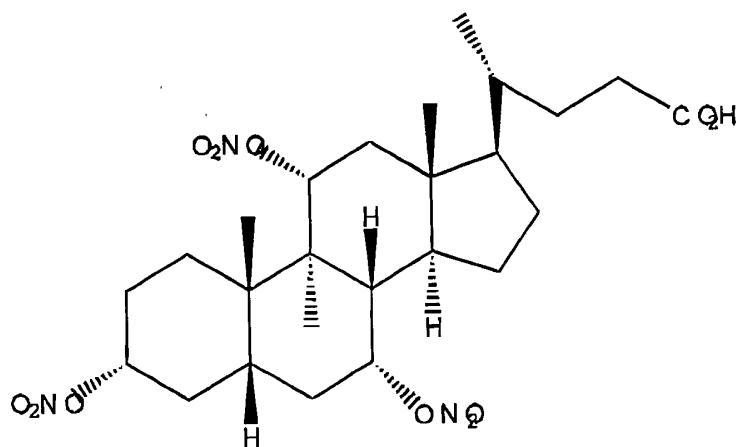
35.   The method of claim 33, wherein the compound has the formula IIIf:
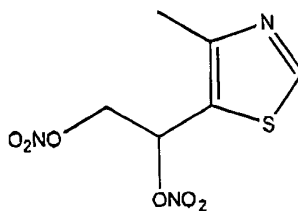
36.   A method of providing sedation or mitigating anxiety in a subject in need thereof, comprising administering to a subject an effective amount of a therapeutic compound selected from the group consisting of:

IVa

,

IVb

,

33

IVc

$$\begin{array}{c}\text{O}\\\parallel\\\text{—CH}_2\text{—P—OCH}_2\text{CH}_3\\\vert\\\text{OCH}_2\text{CH}_3\end{array}$$

—ONO$_2$

—ONO$_2$

,

IVd

—S$_2$O$_3$Na

—ONO$_2$

—ONO$_2$

,

IVe

—S$_2$O$_3$Na

—ONO$_2$

,

IVf

O$_2$NO

,

IVg

O$_2$NO

,

IVh

O$_2$NO

,

IVi

CN

ONO$_2$

ONO$_2$

,

IVj

Br

ONO$_2$

ONO$_2$

,

IVk

,

IVl

,

IVm

SO$_2$Ph

ONO$_2$

ONO$_2$

,

IVn

SCN

ONO$_2$

,

IVo

,

35

IVp

IVq

IVr

IVs   , and

IVt
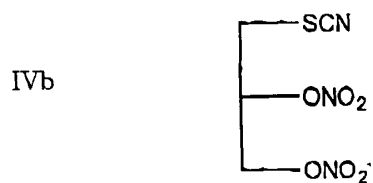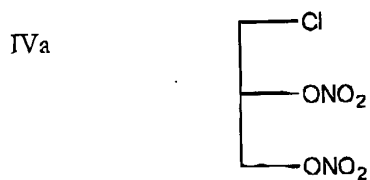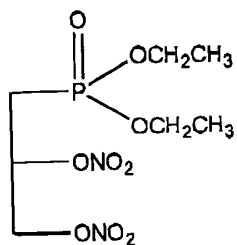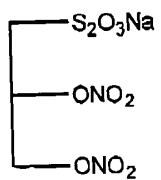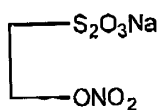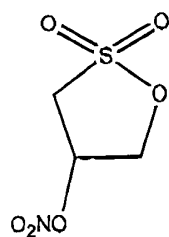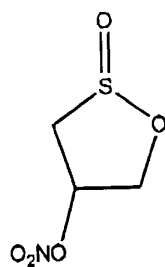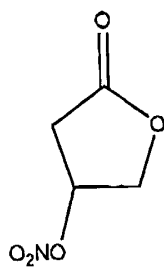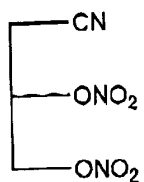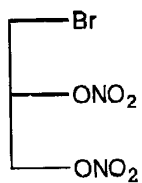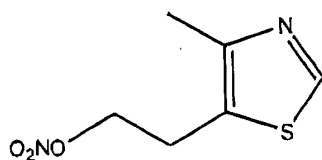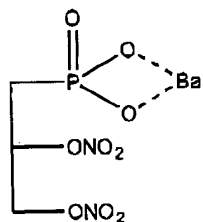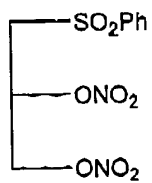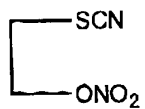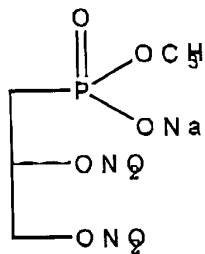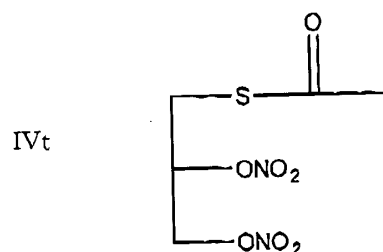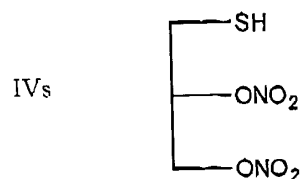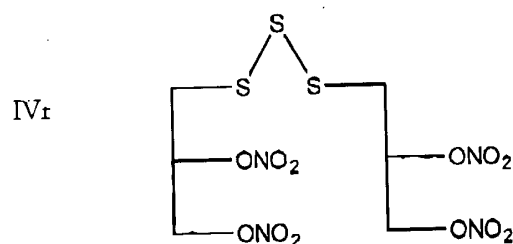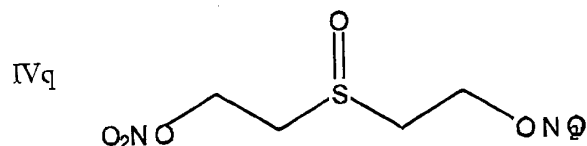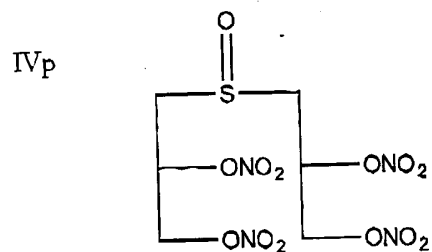
37.   A method of providing sedation in a subject in need thereof, comprising administering to a subject an effective amount of a therapeutic compound having the formula IVk:
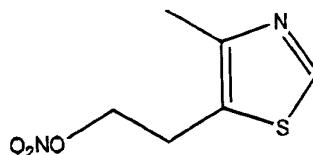
38.   A method of mitigating anxiety in a subject in need thereof, comprising administering to a subject an effective amount of a therapeutic compound selected from the group consisting of:

Va

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Vb

,

Vc

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Vd

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Ve

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Vf

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37
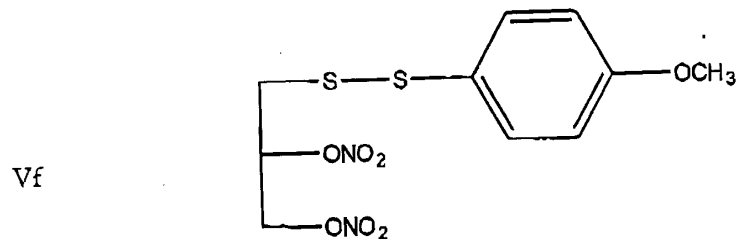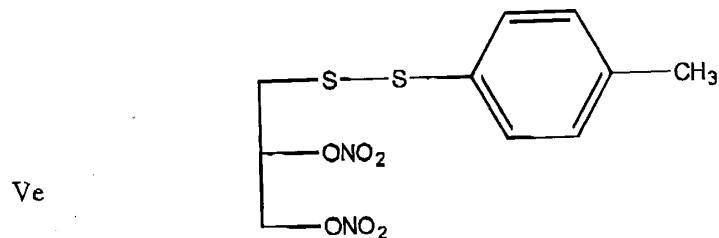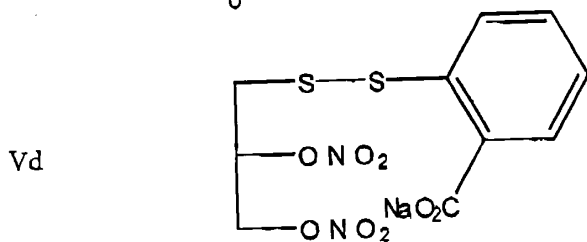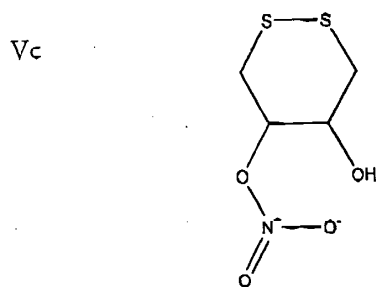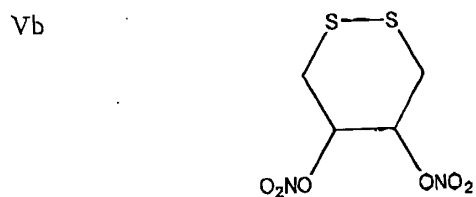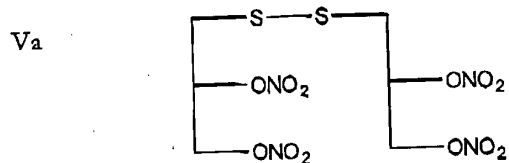
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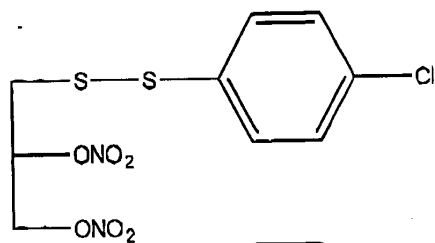
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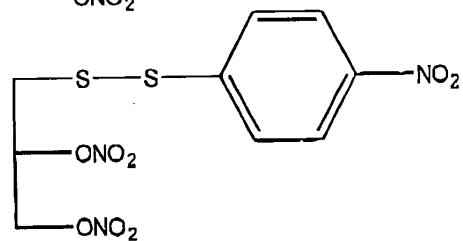
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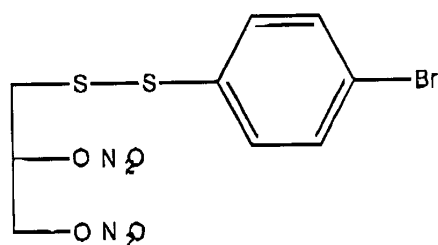
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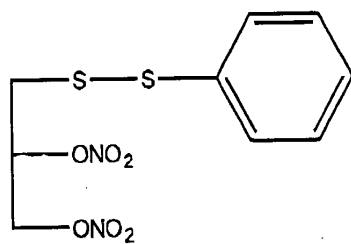
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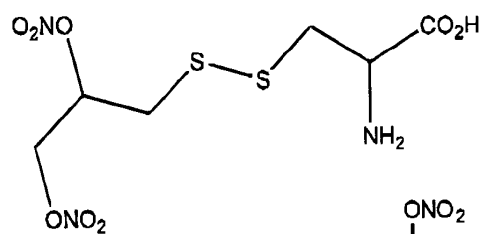
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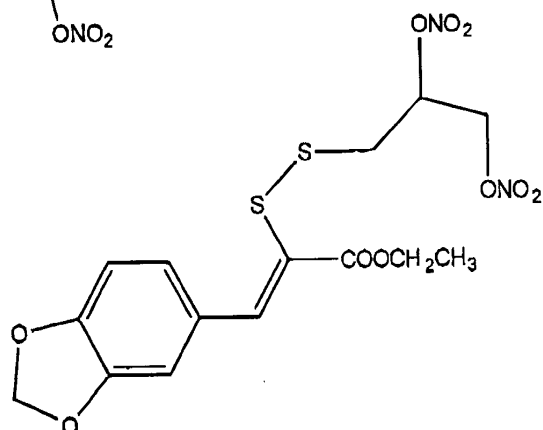
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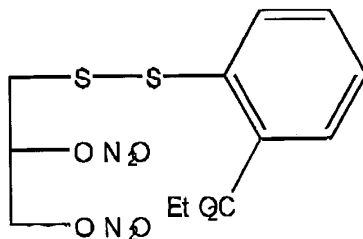
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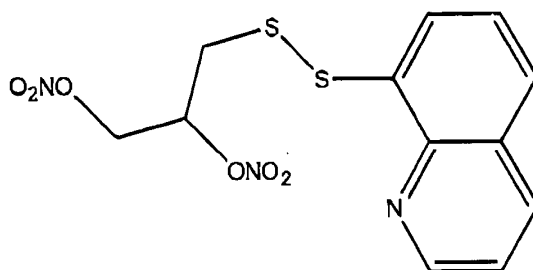
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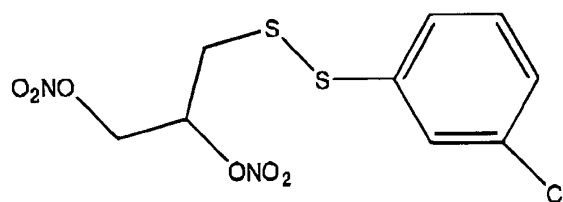
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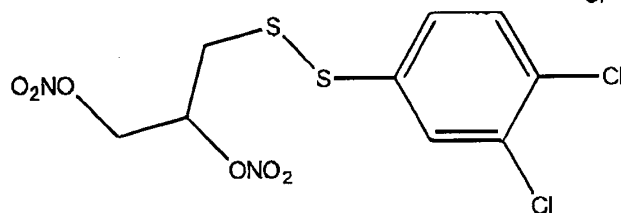
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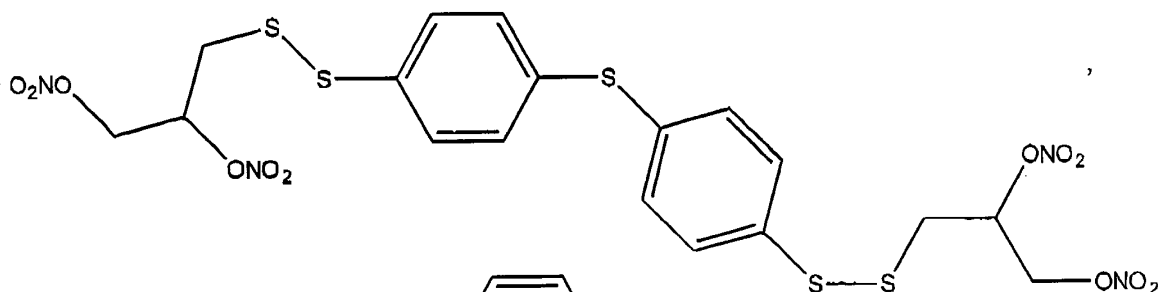
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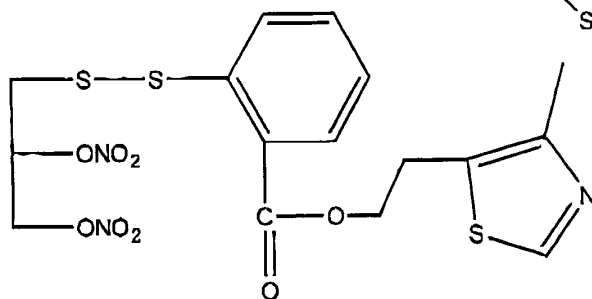
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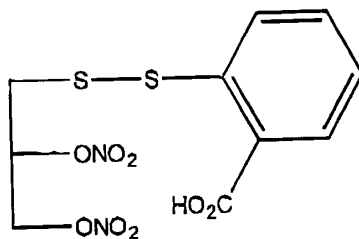
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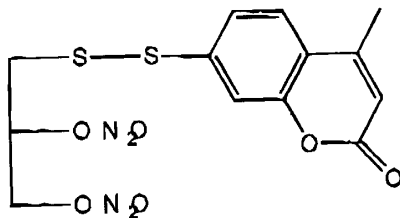
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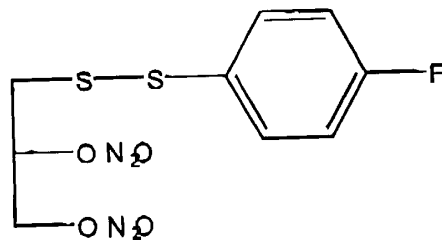
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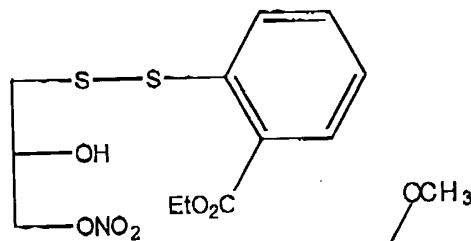
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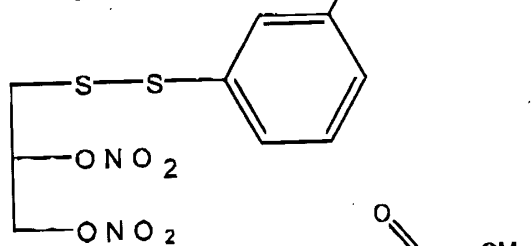
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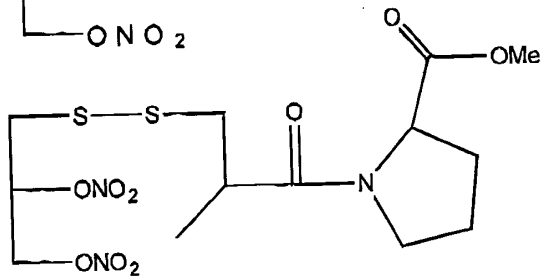
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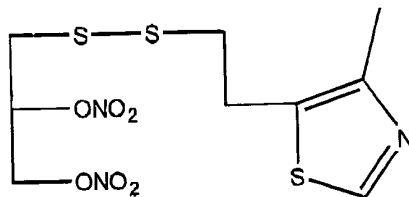
Vz

Vaa

Vab

Vac

Vad

Vae

Vaf

$$\begin{array}{c} S-S-\text{phenyl} \\ -ONO_2 \\ -ONO_2 \end{array}$$, and

the ring bears a $CONH_2$ group

Vag

$$\begin{array}{c} S-S-\text{phenyl} \\ -ONO_2 \\ -ONO_2 \end{array}$$

with $O-C(=O)$ ... $O-CH_2CH_2-N(CH_2CH_3)_2$
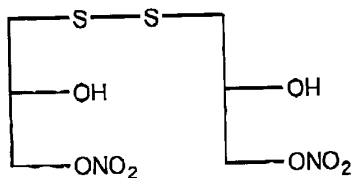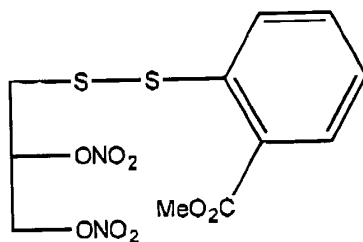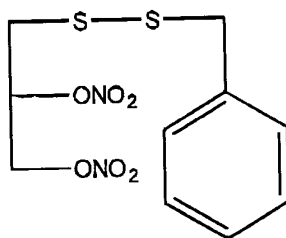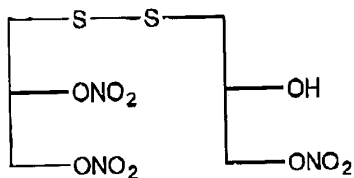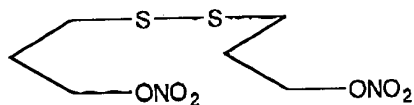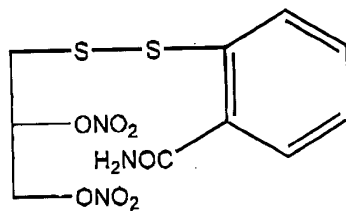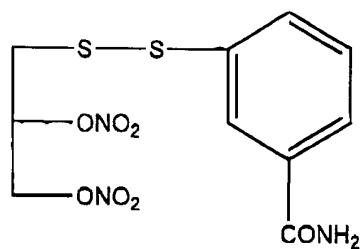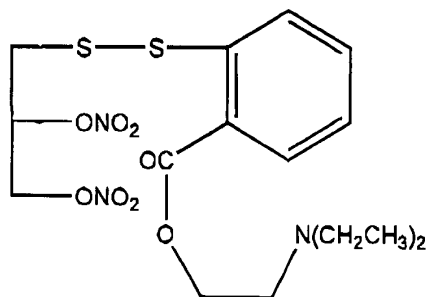
39.   The method of claim 38, wherein the therapeutic compound has the formula Va:

$$\begin{array}{c} S-S \\ -ONO_2 \quad -ONO_2 \\ -ONO_2 \quad -ONO_2 \end{array}$$

40.   A method of mitigating anxiety in a subject in need thereof, comprising administering to a subject an effective amount of a therapeutic compound having the formula IVr:

$$\begin{array}{c} S \\ S \quad S \\ -ONO_2 \quad -ONO_2 \\ -ONO_2 \quad -ONO_2 \end{array}$$

42

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Basic & Clinical Pharmacology

Eighth Edition

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Department of Cellular and Molecular Pharmacology
University of California, San Francisco

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22

Sedative-Hypnotic Drugs

Anthony J. Trevor, PhD, & Walter L. Way, MD

Assignment of a drug to the sedative-hypnotic class indicates that its major therapeutic use is to cause sedation (with concomitant relief of anxiety) or to encourage sleep. There is considerable chemical variation within this group. so this is an example of drug classification based on clinical uses rather than on similarities in chemical structures or mechanisms of action. Anxiety states and sleep disorders are common problems, and sedative-hypnotics are among the most widely prescribed drugs worldwide.

I. BASIC PHARMACOLOGY OF SEDATIVE-HYPNOTICS

An effective sedative (anxiolytic) agent should reduce anxiety and exert a calming effect with little or no effect on motor or mental functions. The degree of central nervous system depression caused by a sedative should be the minimum consistent with therapeutic efficacy. A **hypnotic** drug should produce drowsiness and encourage the onset and maintenance of a state of sleep* that as far as possible resembles the natural sleep state. Hypnotic effects involve more pronounced depression of the central nervous system than sedation. and this can be achieved with most sedative drugs simply by increasing the dose.

Graded dose-dependent depression of central nervous system function is a characteristic of sedative-hypnotics. However, individual drugs differ in the relationship between the dose and the degree of central nervous system depression. Two examples of such dose-response relationships are shown in Figure 22-1. The linear slope for drug A is typical of many of the older sedative-hypnotics. including the barbiturates and alcohols. With such drugs, an increase in

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* We use the word "hypnosis" here in the sense of "sleep" (Gk *hypnos* "sleep") and not in its original (nineteenth century) sense of "a trance-like state resembling sleep."

dose above that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, sedative-hypnotics may depress respiratory and vasomotor centers in the medulla. leading to coma and death. Deviations from a linear dose-response relationship, as shown for drug B, will require proportionately greater dosage increments in order to achieve central nervous system depression more profound than hypnosis. This appears to be the case for most drugs of the benzodiazepine class. and the greater margin of safety this offers is an important reason for their extensive clinical use to treat anxiety states and sleep disorders.

CHEMICAL CLASSIFICATION

The benzodiazepines (Figure 22-2) are the most important sedative-hypnotics. All of the structures shown are 1,4-benzodiazepines. and most contain a carboxamide group in the 7-membered heterocyclic ring structure. A substituent in the 7 position. such as a halogen or a nitro group. is required for sedative-hypnotic activity. The structures of triazolam and alprazolam include the addition of a triazole ring at the 1,2-position. and such drugs are sometimes referred to as triazolobenzodiazepines.

The chemical structures of some older and less commonly used sedative-hypnotics are shown in Figure 22-3. The motivation to develop the benzodiazepines and other newer sedative-hypnotics can be attributed to efforts to avoid undesirable features of the barbiturates. including their potential for inducing psychologic and physiologic dependence. Such efforts have not always been successful. For example. the piperidinediones (glutethimide, others). introduced as "nonbarbiturate sedative-hypnotics." are in fact chemically related to and virtually indistinguishable from barbiturates in their pharmacologic properties. The propanediol carbamates such as meprobamate are of distinctive chemical structure but are practically equiv-
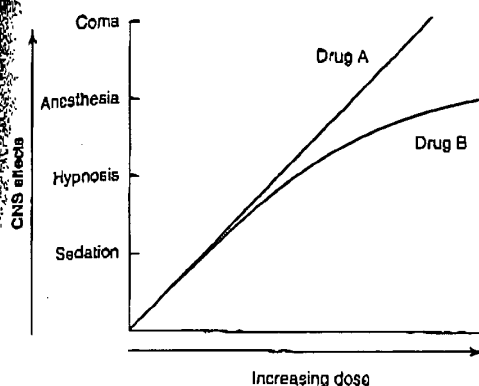
Figure 22-1. Dose-response curves for two hypothetical sedative-hypnotics.

alent to barbiturates in their pharmacologic effects, and their clinical use is rapidly declining. The sedative-hypnotic class also includes compounds of simple chemical structure, including alcohols (ethanol, chloral hydrate) and the cyclic ethers. Chloral hydrate and its congeners, such as trichloroethanol, together with paraldehyde (not shown), continue to be used, particularly in institutionalized patients. Several drugs with novel chemical structures have been introduced recently. Buspirone, an azaspirodecanedione, is an anxiolytic agent that has actions different from those of conventional sedative-hypnotic drugs. Zolpidem (an imidazopyridine) and zaleplon (a pyrazolopyrimidine), while structurally unrelated to benzodiazepines, are hypnotic drugs capable of interaction with benzodiazepine receptors.
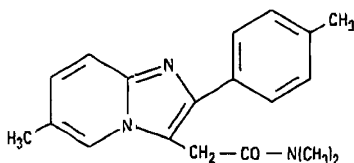
Zolpidem
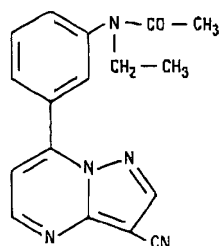
Zaleplon

Other classes of drugs not included in Figure 22-3 may exert sedative effects. For example, β-blocking drugs are effective in certain anxiety states and functional disorders, particularly those in which somatic and autonomic symptoms are prominent. Clonidine, a partial agonist at α_2 receptors, including presynaptic adrenoceptors in the brain, also has anxiolytic properties. Sedative effects can also be obtained with antipsychotic tranquilizers, tricyclic antidepressant drugs, and certain antihistaminic agents. As discussed in other chapters, these agents differ from conventional sedative-hypnotics in both their effects and their major therapeutic uses. Most importantly, they do not produce general anesthesia, and they have low abuse liability. Since they commonly exert marked effects on the peripheral autonomic nervous system, they are sometimes referred to as "sedative-autonomic" drugs. Compounds of the antihistaminic type are present in a number of over-the-counter sleep preparations, in which their autonomic properties as well as their long duration of action can result in adverse effects.

THE BENZODIAZEPINES & BARBITURATES

Pharmacokinetics

A. Absorption: When used to treat anxiety or sleep disorders, sedative-hypnotics are usually given orally. The rates of oral absorption of benzodiazepines differ depending on a number of factors, including lipophilicity. Oral absorption of triazolam is extremely rapid, and that of diazepam and the active metabolite of clorazepate is more rapid than other commonly used benzodiazepines. Clorazepate is converted to its active form, desmethyldiazepam (nordiazepam), by acid hydrolysis in the stomach. Oxazepam, lorazepam, and temazepam are absorbed at slower rates than other benzodiazepines. The bioavailability of several benzodiazepines, including chlordiazepoxide and diazepam, may be unreliable after intramuscular injection. The barbiturates are usually absorbed very rapidly into the blood following oral administration.

B. Distribution: Transport of a sedative-hypnotic in the blood is a dynamic process in which drug molecules enter and leave tissues at rates dependent upon blood flow, concentration gradients, and permeabilities. Lipid solubility plays a major role in determining the rate at which a particular sedative-hypnotic enters the central nervous system. For example, diazepam and triazolam are more lipid-soluble than chlordiazepoxide and lorazepam; thus, the central nervous system actions of the latter drugs are slower in onset. The thiobarbiturates (eg, thiopental), in which the oxygen on C_2 is replaced by sulfur, are very lipid-soluble, and a high rate of entry into the central nervous system contributes to the rapid onset of their

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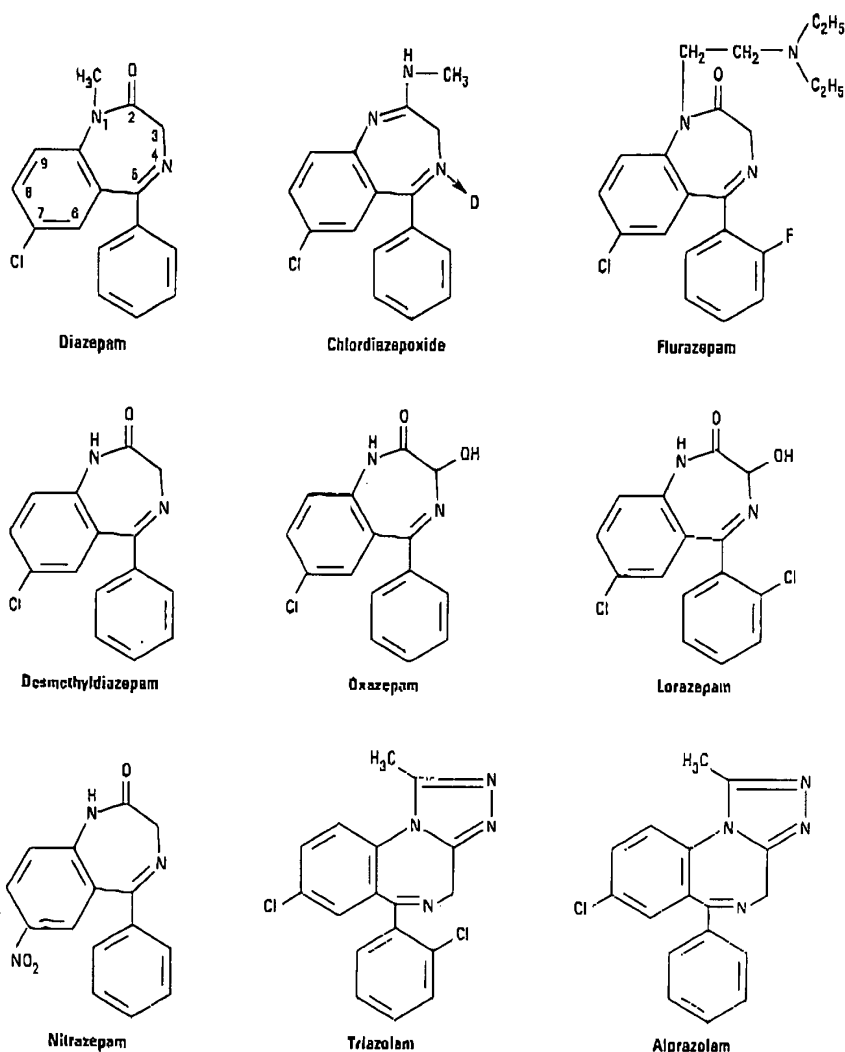
Figure 22-2. Chemical structures of benzodiazepines.

central effects (see Chapter 25). In contrast, meprobamate has quite low solubility in lipids and penetrates the brain slowly even when given intravenously.

Redistribution of drug from the central nervous system to other tissues is an important feature of the biodisposition of sedative-hypnotics. Classic studies on the thiobarbiturates have shown that they are rapidly redistributed from the brain, first to highly perfused tissues such as skeletal muscle and subsequently to poorly perfused adipose tissue. These processes contribute to the termination of their major central nervous system effects. This may also be the case for other sedative-hypnotics, including the benzodiazepines, where the rate of metabolic transformation and elimination in humans is much too slow

to account for the relatively short time required for dissipation of major pharmacologic effects.

All sedative-hypnotics cross the placental barrier during pregnancy. The rate at which maternal and fetal blood concentrations equilibrate is slower than that for the maternal blood and central nervous system, partly because of lower blood flow to the placenta. Nonetheless, if sedative-hypnotics are given in the predelivery period, they may contribute to the depression of neonatal vital functions. Sedative-hypnotics are detectable in breast milk and may exert depressant effects on central nervous system function in the nursing infant.

Benzodiazepines and most other sedative-hypnotics bind extensively to plasma proteins. For exam-
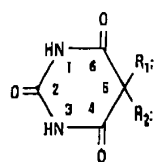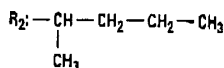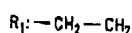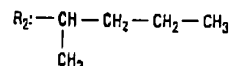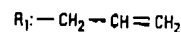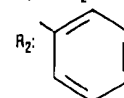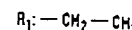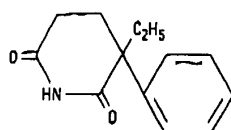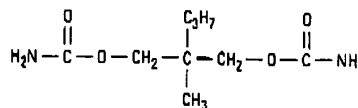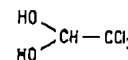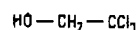
Figure 22–3. Chemical structures of barbiturates and other sedative-hypnotics.

ple, plasma protein binding of benzodiazepines ranges from 60% to over 95%. However, few clinically significant interactions involving sedative-hypnotic drugs appear to be based on competition for common binding sites on the plasma proteins. One exception is chloral hydrate, which transiently increases the anticoagulant effects of warfarin by displacement of the anticoagulant from such binding sites.

C. Biotransformation: Metabolic transformation to more water-soluble metabolites is necessary for clearance from the body of almost all drugs in this class. The microsomal drug-metabolizing enzyme systems of the liver are most important in this regard. Since few sedative-hypnotics are excreted from the body unchanged, the elimination half-life depends mainly on the rate of their metabolic transformation.

1. Benzodiazepines–Hepatic metabolism accounts for the clearance or elimination of all benzodiazepines. The patterns and rates of metabolism depend on the individual drugs. Most benzodiazepines undergo microsomal oxidation (phase I reactions), including N-dealkylation and aliphatic hydroxylation. The metabolites are subsequently conjugated (phase II reactions) by glucuronosyltransferases to form glucuronides that are excreted in the urine. However, many phase I metabolites of benzodiazepines are active, with half-lives greater than the parent drugs.

As shown in Figure 22–4, desmethyldiazepam, which has an elimination half-life of more than 40 hours, is an active metabolite of chlordiazepoxide, diazepam, prazepam, and clorazepate. Desmethyldiazepam in turn is biotransformed to the active compound oxazepam. Other active metabolites of chlor-

diazepoxide include desmethylchlordiazepoxide and demoxepam. While diazepam is metabolized mainly to desmethyldiazepam, it is also converted to temazepam (not shown in Figure 22–4), which is further metabolized in part to oxazepam. Flurazepam, which is used mainly for hypnosis, is oxidized by hepatic enzymes to three active metabolites, desalkylflurazepam, hydroxyethylflurazepam, and flurazepam aldehyde (not shown), which have elimination half-lives ranging from 30 to 100 hours. This may result in unwanted central nervous system depression, including daytime sedation. The triazolobenzodiazepines alprazolam and triazolam undergo alpha-hydroxylation, and the resulting metabolites appear to exert short-lived pharmacologic effects since they are rapidly conjugated to form inactive glucuronides.

The formation of active metabolites has complicated studies on the pharmacokinetics of the benzodiazepines in humans because the elimination half-life of the parent drug may have little relationship to the time course of pharmacologic effects. Those benzodiazepines for which the parent drug or active metabolites have long half-lives are more likely to cause cumulative effects with multiple doses. Cumulative and residual effects such as excessive drowsiness appear to be less of a problem with such drugs as estazolam, oxazepam, and lorazepam, which have shorter half-lives and are metabolized directly to inactive glucuronides. Some pharmacokinetic properties of selected benzodiazepines are listed in Table 22–1.

2. Barbiturates–With the exception of phenobarbital, only insignificant quantities of the barbiturates are excreted unchanged. The major metabolic

Chlordiazepoxide   Diazepam   Prazepam   Clorazepate (Inactive)

Desmethylchlordiazepoxide*

Demoxepam* ⟶ Desmethyldiazepam*   **Alprazolam and triazolam**

Oxazepam*   Alpha-hydroxy metabolites*

Hydroxyethyl-flurazepam*

Flurazepam   CONJUGATION ◀—— Lorazepam

Desalkyl-flurazepam*

URINARY EXCRETION
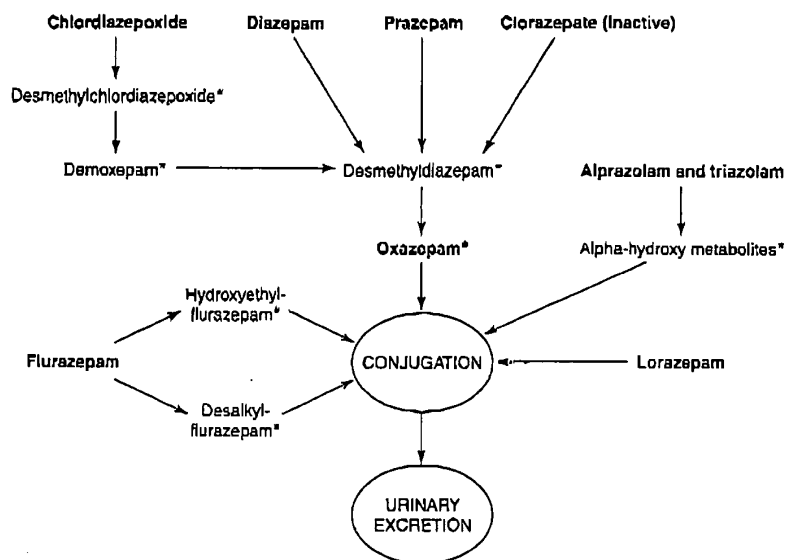
Figure 22–4. Biotransformation of benzodiazepines. (Boldface, drugs available for clinical use; *, active metabolite.)

pathways involve oxidation by hepatic enzymes of chemical groups attached to C_5, which are different for the individual barbiturates. The alcohols, acids, and ketones formed appear in the urine as glucuronide conjugates. With very few exceptions, the metabolites of the barbiturates lack pharmacologic activity. The overall rate of hepatic metabolism in humans depends on the individual drug but (with the

exception of the thiobarbiturates) is usually slow. The elimination half-lives of secobarbital and pentobarbital range from 18 to 48 hours in different individuals. The elimination half-life of phenobarbital in humans is 4–5 days. Multiple dosing with these agents can lead to cumulative effects.

D. Excretion: The water-soluble metabolites of benzodiazepines and other sedative-hypnotics are ex-

Table 22–1. Pharmacokinetic properties of benzodiazepines in humans.

Drug	Peak Blood Level (hours)	Elimination Half-Life[1] (hours)	Comments
Alprazolam	1–2	12–15	Rapid oral absorption
Chlordiazepoxide	2–4	15–40	Active metabolites; erratic bioavailability from IM injection
Clorazepate	1–2 (nordiazepam)	50–100	Prodrug: hydrolyzed to active form in stomach
Diazepam	1–2	20–80	Active metabolites: erratic bioavailability from IM injection
Estazolam	2	10–24	No active metabolites
Flurazepam	1–2	40–100	Active metabolites with long half-lives
Lorazepam	1–6	10–20	No active metabolites
Oxazepam	2–4	10–20	No active metabolites
Prazepam	1–2	50–100	Active metabolites with long half-lives
Quazepam	2	30–100	Active metabolites with long half-lives
Temazepam	2–3	10–40	Slow oral absorption
Triazolam	1	2–3	Rapid onset; short duration of action

[1]Includes half-lives of major metabolites.

creted mainly via the kidney. In most cases, changes in renal function do not have a marked effect on the elimination of parent drugs. Phenobarbital is excreted unchanged in the urine to a certain extent (20–30% in humans), and its elimination rate can be increased significantly by alkalinization of the urine. This is partly due to increased ionization at alkaline pH, since phenobarbital is a weak acid with a pK_a of 7.4. Only trace amounts of the benzodiazepines and less than 10% of a hypnotic dose of meprobamate appear in the urine unchanged.

E. Factors Affecting Biodisposition: The biodisposition of sedative-hypnotics can be influenced by several factors, particularly alterations in hepatic function resulting from disease, old age, or drug-induced increases or decreases in microsomal enzyme activities.

As described in Chapter 4, decreased hepatic function may result in reduction of the clearance of drugs metabolized via oxidative pathways. Many of the benzodiazepines, almost all of the barbiturates, the piperidinediones, and meprobamate fall into this category. In very old patients and in patients with severe liver disease, the elimination half-lives of these drugs are usually increased significantly. In such cases, multiple normal doses of these sedative-hypnotics often result in excessive central nervous system effects. Thus, it is common practice to reduce the dosage of such sedative-hypnotics in patients who are elderly or who may have limited hepatic function. Metabolism involving glucuronide conjugation appears to be less affected by old age or liver disease than oxidative metabolism.

The activity of hepatic microsomal drug-metabolizing enzymes may be increased in patients exposed to certain older sedative-hypnotics on a chronic basis (enzyme induction; see Chapter 4). Drugs with long elimination half-lives such as phenobarbital and meprobamate are most likely to cause this effect and result in an increase in their own hepatic metabolism as well as that of certain other drugs. Self-induction of metabolism is a possible but poorly documented mechanism that contributes to the development of tolerance to sedative-hypnotics. Increased biotransformation of other pharmacologic agents as a result of enzyme induction by barbiturates is a potential mechanism underlying drug interactions (Appendix II). In contrast, the benzodiazepines do not change hepatic drug-metabolizing enzyme activity with continuous use.

Pharmacodynamics of Benzodiazepines & Barbiturates

A. Molecular Pharmacology of the GABA$_A$ Receptor: The benzodiazepines, the barbiturates, and the imidazopyridines bind to molecular components of the GABA$_A$ receptor present in neuronal membranes in the central nervous system. This ionotropic receptor, a transmembrane heteroligomeric

protein that functions as a chloride ion channel, is activated by the inhibitory neurotransmitter GABA.

Molecular cloning techniques show the GABA$_A$ receptor chloride ion channel macromolecular complex to have a pentameric structure assembled from five subunits selected from eight polypeptide classes (alpha, beta, gamma, delta, epsilon, pi, rho, and theta). Different subunits of several of these classes have been characterized, eg, six different alpha, four beta, and three gamma. Such multiplicity accounts for a large number of putative receptor isoforms. Reconstitution of the GABA$_A$ receptor chloride ion channel complex has revealed that combinations of the three major subunits—alpha, beta, and gamma—are essential for normal physiologic and pharmacologic functions. The role of other subunits in modulating the activity of the channel awaits further study. GABA$_A$ receptors in different areas of the central nervous system contain different combinations of the essential subunits conferring different pharmacologic properties on such GABA$_A$ receptor subtypes.

BENZODIAZEPINE RECEPTOR HETEROGENEITY

Benzodiazepine receptors in the central nervous system have been classified as BZ_1 (also called omega$_1$) and BZ_2 (omega$_2$) subtypes on the basis of their relative affinities for different benzodiazepines and for nonbenzodiazepine drugs that appear to act via benzodiazepine receptors. Differences in binding affinities of receptor ligands are due to heterogeneity in GABA$_A$ receptor subunit composition. Activators of BZ_1 receptors have a high affinity for GABA receptors containing the alpha$_1$ subunit and a very low affinity for receptors containing an alpha$_5$ subunit (corresponding to one type of BZ_2 receptor). Most benzodiazepines used clinically are able to interact with both BZ_1 and BZ_2 receptor subtypes, but zaleplon and zolpidem are BZ_1-selective. As noted in the text, zolpidem exerts hypnotic activity with minimal muscle relaxing or anticonvulsant effects and with less amnestic effects than benzodiazepines. Thus, the spectrum of pharmacologic actions elicited by drugs that modulate GABA actions is influenced by the composition of the subunits assembled to form the GABA$_A$ receptor. With further molecular characterization of these ligand-binding sites on the various GABA$_A$ receptors in different regions of the brain, it may be possible to design drugs that are more selective than currently available sedative-hypnotics.

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Sensitivity of the reconstituted receptor-chloride ion channel complex to benzodiazepines is determined by particular alpha and gamma subunit variants. Isoforms containing alpha$_1$, beta$_2$, and gamma$_2$ subunits, which appear to be most sensitive, are widely distributed in the central nervous system. Several amino acid residues of the alpha$_1$ subunit have been identified as crucial for benzodiazepine sensitivity, especially the serine at position 204. A change in residue 77 of the gamma$_2$ subunit prevents benzodiazepine binding to the receptor-ion channel complex. Benzodiazepine receptor heterogeneity occurs (see box: Benzodiazepine Receptor Heterogeneity) since the drugs also bind to isoforms that contain the alpha$_5$ subunit, eg, those identified in brain hippocampal neurons. A model of the hypothetical GABA-BZ receptor-chloride ion channel macromolecular complex is shown in Figure 22-5.

B. Neuropharmacology: Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Electrophysiologic
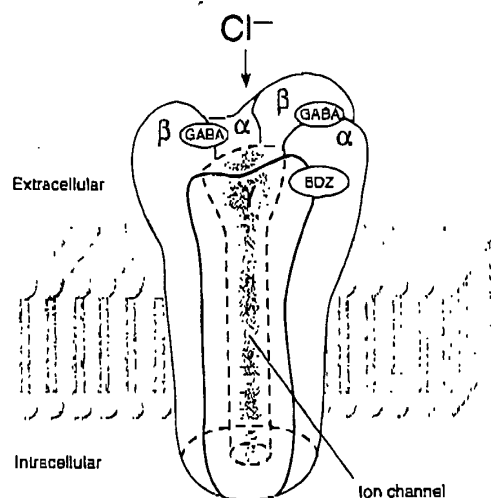
Figure 22-5. A model of the GABA$_A$ receptor-chloride ion channel macromolecular complex (many others could be proposed). A heteroligomeric glycoprotein, the complex consists of five or more membrane-spanning subunits. Multiple forms of alpha, beta, and gamma subunits are arranged in different pentameric combinations so that GABA$_A$ receptors exhibit molecular heterogeneity. GABA appears to interact with alpha or beta subunits triggering chloride channel opening with resultant membrane hyperpolarization. Binding of benzodiazepines to gamma subunits or to an area of the alpha unit influenced by the gamma unit facilitates the process of channel opening but does not directly initiate chloride current. (Modified and reproduced, with permission, from Zorumsky CF, Isenberg KE: Insights into the structure and function of GABA-benzodiazepine receptors: Ion channels and psychiatry. Am J Psychiatry 1991;148:162.)

studies have shown that benzodiazepines potentiate GABAergic inhibition at all levels of the neuraxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex, and cerebral cortex. Benzodiazepines appear to increase the efficiency of GABAergic synaptic inhibition (via membrane hyperpolarization), which leads to a decrease in the firing rate of critical neurons in many regions of the brain. The benzodiazepines do not substitute for GABA but appear to enhance GABA's effects without directly activating GABA receptors or opening the associated chloride channels. The enhancement in chloride ion conductance induced by the interaction of benzodiazepines with GABA takes the form of an increase in the *frequency* of channel-opening events (Figure 22-6). This effect may be due in part to enhanced receptor affinity for GABA.

Barbiturates also facilitate the actions of GABA at multiple sites in the central nervous system, but—in contrast to benzodiazepines—they appear to increase the *duration* of the GABA-gated channel openings (Figure 22-6). At high concentrations, the barbiturates may also be GABA-mimetic, directly activating chloride channels. These effects involve a binding site or sites distinct from the benzodiazepine binding site. Barbiturates are less selective in their actions than benzodiazepines, since they also depress the actions of excitatory neurotransmitters and exert nonsynaptic membrane effects in parallel with their effects on GABA neurotransmission. This multiplicity of sites of action of barbiturates may be the basis for their ability to induce full surgical anesthesia (see Chapter 25) and for their more pronounced central depressant effects (which result in their low margin of safety) compared to benzodiazepines.

C. Benzodiazepine Receptor Ligands: Three types of ligand-benzodiazepine receptor interactions have been reported: (1) **Agonists** facilitate GABA action and act as positive allosteric modulators of receptor function. These actions are typically produced by the clinically useful benzodiazepines, which exert anxiolytic and anticonvulsant effects. Zolpidem and zaleplon are selective agonists at the BZ$_1$ (omega$_1$) receptor subtype. Endogenous agonist ligands for the BZ receptors have been proposed, since benzodiazepine-like chemicals have been isolated from brain tissue of animals never exposed to these drugs, and benzodiazepine-like immunoreactivity has been detected in human brains stored in paraffin 15 years before the first benzodiazepine drug was synthesized. Nonbenzodiazepine molecules that have affinity for benzodiazepine receptors have also been detected in human brain. Such "endozepines" facilitate GABA-mediated chloride channel gating in cultured neurons. (2) **Antagonists** are typified by the synthetic benzodiazepine derivative **flumazenil**, which blocks the actions of benzodiazepines and zolpidem but does not antagonize the actions of barbiturates, meprobamate, or ethanol. Certain endogenous com-
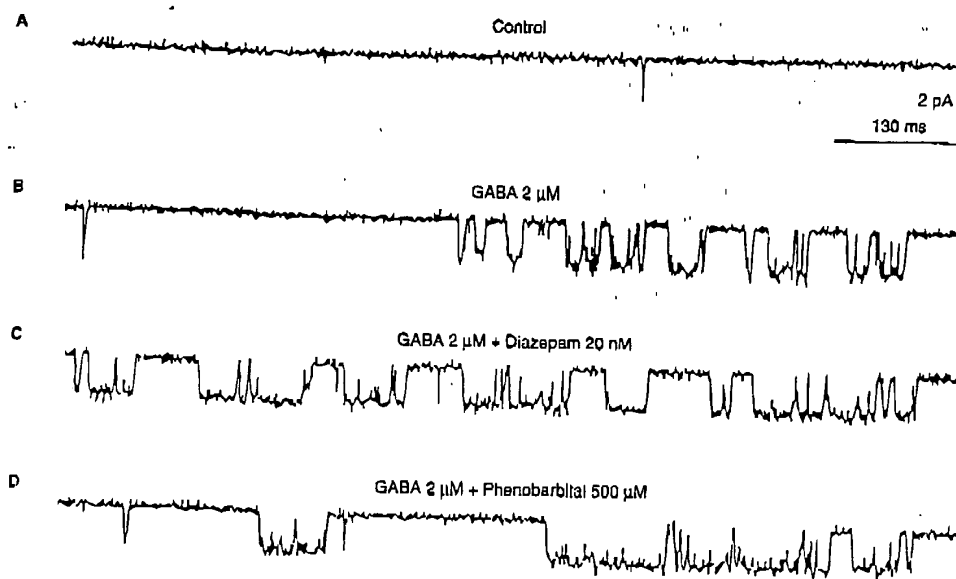
Figure 22-6. Patch-clamp recording of single-channel GABA-evoked currents in mouse spinal cord neurons. *A:* Control. *B:* Channel opening (downward deflections) elicited by GABA. *C:* Diazepam increases the frequency of channel opening without marked effects on duration of openings. *D:* Phenobarbital prolongs the duration of channel openings without marked effects on frequency. (Reproduced, with permission, from Twyman RE et al: Differential regulation of GABA receptor channels by diazepam and phenobarbital. Ann Neurol 1989;25:213.)

pounds, eg. diazepam-binding inhibitor (DBI), are also capable of blocking the interaction of benzodiazepines with benzodiazepine receptors. (3) **Inverse agonists** act as negative allosteric modulators of GABA receptor function. Their interaction with benzodiazepine receptors can produce anxiety and seizures, an action that has been demonstrated for several compounds, especially the β-carbolines, eg. *n*-butyl-β-carboline-3-carboxylate (β-CCB). In addition to their direct actions, these molecules can block the effects of benzodiazepines.

The physiologic significance of endogenous modulators of the functions of GABA in the central nervous system remain unclear. To date it has not been established that these putative endogenous ligands of BZ receptors play a role in the control of states of anxiety, sleep patterns, or any other characteristic behavioral expression of central nervous system function.

D. Organ Level Effects:

1. **Sedation**–Sedation can be defined as a suppression of responsiveness to a constant level of stimulation, with decreased spontaneous activity and ideation. These behavioral changes occur at the lowest effective doses of the commonly used sedative-hypnotics, and it is not yet clear whether such antianxiety actions seen clinically are equivalent to or different from sedative effects. In experimental animal models, benzodiazepines and the older sedative-

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THE VERSATILITY OF THE CHLORIDE CHANNEL GABA RECEPTOR COMPLEX

The chloride channel molecule that contains the GABA receptor is one of the most versatile drug-responsive machines in the body. In addition to the benzodiazepines and barbiturates, many other drugs with central nervous system effects bind to this important channel.

Other central nervous system depressants include propofol (an important intravenous anesthetic), alfaxolone (a steroid anesthetic), certain gaseous anesthetics, several new anticonvulsants (gabapentin, vigabatrin), and ivermectin (an anthelmintic agent). These agents facilitate or mimic the action of GABA. (It must be noted that it has not been shown that these drugs act exclusively or even primarily by this mechanism.) Central nervous system excitatory agents that act on the chloride channel include picrotoxin and bicuculline. These convulsant drugs block the channel directly (picrotoxin) or interfere with GABA binding (bicuculline).

hypnotic drugs are able to release punishment-suppressed behavior, and this disinhibition has been equated with antianxiety effects. However. the release of previously suppressed behavior may be more relevant to behavioral disinhibitory effects of these drugs, including euphoria, impaired judgment, and loss of self-control, which can occur at dosages in the range of those used for management of anxiety. While most sedative-hypnotic drugs are capable of releasing punishment-suppressed behavior in animals, the benzodiazepines exert such effects at dosages that cause only minor central nervous system depression. Although they have sedative actions, antipsychotic drugs and tricyclic antidepressants are not effective in this experimental model. The benzodiazepines also exert anterograde amnesic effects (inability to remember events occurring during the drug's action) at sedative dosages. Buspirone is the most distinctive drug in terms of antianxiety actions, since these are achieved with minimal effects on psychomotor functions.

2. Hypnosis—By definition. all of the sedative-hypnotics will induce sleep if high enough doses are given. Normal sleep consists of distinct stages. based on three physiologic measures: the electroencephalogram. the electromyogram. and the electronystagmogram (a measure of lateral movements of the eye). Based on the latter, two major categories can be distinguished: non-rapid eye movement (NREM) sleep, which represents approximately 70-75% of total sleep: and rapid eye movement (REM) sleep. REM and NREM sleep occur cyclically over an interval of about 90 minutes. The REM sleep stage is that in which most recallable dreams occur. NREM sleep progresses through four stages (1–4), with the greatest proportion (50%) of sleep being spent in stage 2. This is followed by delta or slow-wave sleep (stages 3 and 4). in which somnambulism and night terrors occur. During slow wave sleep. the secretion of adrenal steroids is at its lowest and secretion of somatotropin is at its highest.

The effects of sedative-hypnotics on the sleep stages have been studied extensively. though often with normal volunteer subjects rather than patients with sleep disorders. The effects observed depend on several factors, including the specific drug. the dose. and the frequency of its administration. While some exceptions exist, the effects of sedative-hypnotics on patterns of normal sleep are as follows: (1) the latency of sleep onset is decreased (time to fall asleep); (2) the duration of stage 2 NREM sleep is increased; (3) the duration of REM sleep is decreased; and (4) the duration of slow-wave sleep is decreased.

More rapid onset of sleep and prolongation of stage 2 are presumably clinically useful effects. However, the significance of sedative-hypnotic drug effects on REM and slow-wave sleep is not clear. Deliberate interruption of REM sleep causes anxiety and irritability followed by a rebound increase in

REM sleep at the end of the experiment. A similar pattern of "REM rebound" can be detected following cessation of drug treatment with most sedative-hypnotics. Despite possible reductions in slow wave sleep there are no reports of disturbances in the secretion of pituitary or adrenal hormones when either barbiturates or benzodiazepines are used as hypnotics. The use of sedative-hypnotics for more than 1–2 weeks leads to some tolerance to their effects on sleep patterns.

3. Anesthesia—As shown in Figure 22–1. certain sedative-hypnotics in high doses will depress the central nervous system to the point known as stage III of general anesthesia (see Chapter 25). However, the suitability of a particular agent as an adjunct in anesthesia depends mainly on the physicochemical properties that determine its rapidity of onset and duration of effect. Among the barbiturates, thiopental and methohexital are very lipid-soluble, penetrating brain tissue rapidly following intravenous administration. Rapid tissue redistribution accounts for the short duration of action of these drugs, which are therefore useful in anesthesia practice.

Certain benzodiazepines, including diazepam and midazolam. are used intravenously in anesthesia (see Chapter 24) but have not proved to be fully successful as agents capable of producing surgical anesthesia by themselves. This statement is supported by the fact that the MAC (minimum alveolar anesthetic concentration, Chapter 25) of another anesthetic cannot be reduced to zero by the substitution of a benzodiazepine. Not surprisingly. benzodiazepines given in large doses as adjuncts to general anesthetics may contribute to a persistent postanesthetic respiratory depression. This is probably related to their relatively long half-lives and the formation of active metabolites.

4. Anticonvulsant effects—Most of the sedative-hypnotics are capable of inhibiting the development and spread of epileptiform activity in the central nervous system. Some selectivity exists in that certain drugs can exert anticonvulsant effects without marked central nervous system depression, so that mentation and physiologic activity are relatively unaffected. Several benzodiazepines, including clonazepam. nitrazepam. lorazepam. and diazepam. have selective actions that are clinically useful in the management of seizure states (see Chapter 24). Of the barbiturates, phenobarbital and metharbital (converted to phenobarbital in the body) are effective in the treatment of generalized tonic-clonic seizures.

5. Muscle relaxation—Some sedative-hypnotics. particularly members of the carbamate and benzodiazepine groups, exert inhibitory effects on polysynaptic reflexes and internuncial transmission and at high doses may also depress transmission at the skeletal neuromuscular junction. Somewhat selective actions of this type that lead to muscle relaxation can be readily demonstrated in animals and have led to

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claims of usefulness for relaxing contracted voluntary muscle in joint disease or muscle spasm (see Clinical Pharmacology).

6. Effects on respiration and cardiovascular function—At hypnotic doses in healthy patients, the effects of sedative-hypnotics on respiration are comparable to changes during natural sleep. However, sedative-hypnotics even at therapeutic doses can produce significant respiratory depression in patients with pulmonary disease. Effects on respiration are dose-related, and depression of the medullary respiratory center is the usual cause of death due to overdose of sedative-hypnotics.

At doses up to those causing hypnosis, no significant effects on the cardiovascular system are observed in healthy patients. However, in hypovolemic states, congestive heart failure, and other diseases that impair cardiovascular function, normal doses of sedative-hypnotics may cause cardiovascular depression, probably as a result of actions on the medullary vasomotor centers. At toxic doses, myocardial contractility and vascular tone may both be depressed by central and peripheral effects, leading to circulatory collapse. Respiratory and cardiovascular effects become more apparent when sedative-hypnotics are given intravenously.

Tolerance; Psychologic & Physiologic Dependence

Tolerance—decreased responsiveness to a drug following repeated exposure—is a common feature of sedative-hypnotic use. It may result in an increase in the dose needed to maintain symptomatic improvement or to promote sleep. It is important to recognize that partial cross-tolerance occurs between the sedative-hypnotics described here and also with ethanol (Chapter 23)—a feature of some clinical importance, as explained below. The mechanisms responsible for tolerance to sedative-hypnotics are not well understood. An alteration in the rate of metabolic inactivation with chronic administration may be partly responsible (metabolic tolerance) in the case of barbiturates, but changes in responsiveness of the central nervous system (pharmacodynamic tolerance) are of greater importance for most sedative-hypnotics. In the case of benzodiazepines, the development of tolerance in animals is associated with down-regulation of brain benzodiazepine receptors.

The perceived desirable properties of relief of anxiety, euphoria, disinhibition, and promotion of sleep have led to the compulsive misuse of virtually all sedative-hypnotics. For this reason, most sedative-hypnotic drugs are classified as Schedule III or Schedule IV drugs for prescribing purposes. (See Chapter 32 for a detailed discussion of drug abuse.) The consequences of abuse of these agents can be defined in both psychologic and physiologic terms. The psychologic component may initially parallel simple neurotic behavior patterns difficult to differentiate

from those of the inveterate coffee drinker or cigarette smoker. When the pattern of sedative-hypnotic use becomes compulsive, more serious complications develop, including physiologic dependence and tolerance.

Physiologic dependence can be described as an altered physiologic state that requires continuous drug administration to prevent the appearance of an abstinence or withdrawal syndrome. As described more fully later, in the case of sedative-hypnotics this syndrome is characterized by states of increased anxiety, insomnia, and central nervous system excitability that may progress to convulsions. Most sedative-hypnotics—including benzodiazepines—are capable of causing physiologic dependence when used on a chronic basis. However, the severity of withdrawal symptoms differs between individual drugs and depends also on the magnitude of the dose used immediately prior to cessation of use. When higher doses of sedative-hypnotics are used, abrupt withdrawal leads to more serious withdrawal signs. Differences in the severity of withdrawal symptoms between individual sedative-hypnotics relate in part to half-life, since drugs with long half-lives are eliminated slowly enough to accomplish gradual withdrawal with few physical symptoms. The use of drugs with very short half-lives for hypnotic effects may lead to signs of withdrawal even between doses. For example, triazolam, a benzodiazepine with a half-life of about 4 hours, has been reported to cause daytime anxiety when used to treat sleep disorders.

BENZODIAZEPINE ANTAGONISTS: FLUMAZENIL

Flumazenil is one of several 1,4-benzodiazepine derivatives with high affinity for the benzodiazepine receptor that act as competitive antagonists. It is the only benzodiazepine receptor antagonist available for clinical use at present. It blocks many of the actions of benzodiazepines (and imidazopyridines) but does not antagonize the central nervous system effects of other sedative-hypnotics, ethanol, opioids, or general anesthetics. Flumazenil is approved for use in reversing the central nervous system depressant effects of benzodiazepine overdose and to hasten recovery following use of these drugs in anesthetic and diagnostic procedures. While the drug reverses the sedative effects of benzodiazepines, antagonism of benzodiazepine-induced respiratory depression is less predictable. When given intravenously, flumazenil acts rapidly but has a short half-life (0.7–1.3 hours) due to rapid hepatic clearance. Since all benzodiazepines have a longer duration of action than flumazenil, sedation commonly recurs, requiring repeated administration of the antagonist.

Adverse effects of flumazenil include agitation, confusion, dizziness, and nausea. Flumazenil may

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cause a severe precipitated abstinence syndrome in patients who have developed physiologic benzodiazepine dependence. In patients who have ingested benzodiazepines with tricyclic antidepressants, seizures and cardiac arrhythmias may occur following flumazenil administration. Transient improvement in mental status has been reported with flumazenil when used in patients with hepatic encephalopathy.

NEWER DRUGS FOR ANXIETY & SLEEP DISORDERS

Although the benzodiazepines continue to be the agents of choice in the treatment of most anxiety states and for insomnia, their pharmacologic effects include daytime sedation and drowsiness, synergistic depression of the central nervous system with other drugs (especially alcohol), and the possibility of psychologic and physiologic dependence with repeated use. Anxiolytic drugs that act through non-GABAergic systems might have a reduced propensity for such actions. Several new nonbenzodiazepines, including buspirone, have such characteristics. In addition, certain imidazopyridines, including zolpidem, may be more selective in their central actions even though they appear to act through benzodiazepine receptors.

Buspirone

Buspirone relieves anxiety without causing marked sedative or euphoric effects. Unlike benzodiazepines, the drug has no hypnotic, anticonvulsant, or muscle relaxant properties. Buspirone does not interact directly with GABAergic systems and may exert its anxiolytic effects by acting as a partial agonist at brain $5-HT_{1A}$ receptors. Buspirone-treated patients show no rebound anxiety or withdrawal signs on abrupt discontinuance. The drug is not effective in blocking the acute withdrawal syndrome resulting from abrupt cessation of use of benzodiazepines or other sedative-hypnotics. Buspirone has minimal abuse liability. In contrast to the benzodiazepines, the anxiolytic effects of buspirone may take more than a week to become established, making this drug suitable mainly for generalized anxiety states. The drug is not very effective in panic disorders.

Buspirone is rapidly absorbed orally but undergoes extensive first-pass metabolism via hydroxylation and dealkylation reactions to form several active metabolites. The major metabolite is 1-(2-pyrimidyl)-piperazine (1-PP), which has α_2-adrenoceptor-blocking actions and which enters the central nervous system to reach higher levels than the parent drug. It is not known what role (if any) 1-PP plays in the central actions of buspirone. The elimination half-life of buspirone is 2–4 hours, and liver dysfunction may decrease its clearance. Rifampin, an inducer of cytochrome P450, decreases the half life of buspirone;

inhibitors of CYP3A4 (eg, erythromycin, ketoconazole) increase plasma levels of buspirone.

Buspirone causes less psychomotor impairment than diazepam and does not affect driving skills. The drug does not potentiate the central nervous system depressant effects of conventional sedative-hypnotic drugs, ethanol, or tricyclic antidepressants, and elderly patients do not appear to be more sensitive to its actions. Tachycardia, palpitations, nervousness, gastrointestinal distress, and paresthesias may occur more frequently than with benzodiazepines. Buspirone also causes a dose-dependent pupillary constriction. Blood pressure may be elevated in patients receiving MAO inhibitors. A number of buspirone analogs have been developed (eg, ipsapirone, gepirone, tandospirone) and are under study.

Zolpidem

Zolpidem, an imidazopyridine derivative structurally unrelated to benzodiazepines, has hypnotic actions. The drug binds selectively to the BZ_1 ($omega_1$) subtype of benzodiazepine receptors and facilitates GABA-mediated neuronal inhibition. Like the benzodiazepines, the actions of zolpidem are antagonized by flumazenil. Unlike benzodiazepines, zolpidem has minimal muscle relaxing and anticonvulsant effects. When used for the short-term treatment of insomnia, zolpidem has an efficacy similar to that of hypnotic benzodiazepines. The drug has an onset of action similar to that of flurazepam, but its duration of action is closer to that of triazolam. Zolpidem causes minor effects on sleep patterns at the recommended hypnotic dose but can suppress REM sleep at higher doses. Respiratory depression may occur if large doses of zolpidem are ingested with other central nervous system depressants, including ethanol.

The risk of development of tolerance and dependence with extended use of zolpidem appears to be less than with the use of hypnotic benzodiazepines. Zolpidem is rapidly metabolized to inactive metabolites by the liver via oxidation and hydroxylation. The elimination half-life of the drug is 1.5–3.5 hours, with clearance decreased in elderly patients. Dosage reductions are recommended in patients with hepatic dysfunction, in elderly patients, and in patients taking cimetidine. Rifampin, an inducer of hepatic cytochrome P450, decreases the half-life of zolpidem.

Zaleplon

Zaleplon resembles zolpidem. The drug binds selectively to the BZ_1 receptor subtype, facilitating the inhibitory actions of GABA. Zaleplon is rapidly absorbed from the gastrointestinal tract and has an elimination half-life of about 1 hour. It is metabolized mainly by hepatic aldehyde oxidase and partly by the cytochrome P450 isoform CYP3A4. Dosage

should be reduced in patients with hepatic impairment and in the elderly. Metabolism of zaleplon is inhibited by cimetidine; drugs that induce hepatic CYP3A4 increase the clearance of zaleplon.

Zaleplon decreases sleep latency but has little effect on total sleep time or on sleep architecture. Rapid onset and short duration of action are favorable properties for those patients who have difficulty falling asleep. Amnestic effects and next-day impairment of psychomotor performance may occur, but less commonly than in the case of hypnotic benzodiazepines or zolpidem. Tolerance development and withdrawal symptoms have not been reported, but the use of high doses (twice the recommended dose) has caused rebound insomnia. Zaleplon may potentiate the central nervous system depressant effects of ethanol.

OLDER SEDATIVE-HYPNOTICS

These drugs include alcohols (ethchlorvynol, chloral hydrate), piperidinediones (glutethimide, methyprylon), and carbamates (meprobamate). They are rarely used in therapy, though the low cost of chloral hydrate makes it attractive for institutional use. Little is known about their molecular mechanisms of action. Most of these drugs are biotransformed to more water-soluble compounds by hepatic enzymes. Trichloroethanol is the pharmacologically active metabolite of chloral hydrate and has a half-life of 6–10 hours. However, its toxic metabolite, trichloroacetic acid, is cleared very slowly and can accumulate with the nightly administration of chloral hydrate. Furthermore, recurrent concerns regarding the possible carcinogenicity of chloral hydrate itself—or its metabolites—suggest that this drug should not be used until more data are available.

II. CLINICAL PHARMACOLOGY OF SEDATIVE-HYPNOTICS

TREATMENT OF ANXIETY STATES

The psychologic, behavioral, and physiologic responses that characterize anxiety can take many forms. Typically, the psychic awareness of anxiety is accompanied by enhanced vigilance, motor tension, and autonomic hyperactivity. Before prescribing sedative-hypnotics, one should analyze the patient's symptoms carefully. Anxiety is in many cases secondary to organic disease states—acute myocardial infarction, angina pectoris, gastrointestinal ulcers, etc—which themselves require specific therapy. Another class of secondary anxiety states (situational anxiety) results from circumstances that may have to be dealt with only once or only a few times, including anticipation

of frightening medical or dental procedures and family illness or other tragedy. Even though situational anxiety tends to be self-limiting, the short-term use of sedative-hypnotics may be appropriate for the treatment of this and certain disease-associated anxiety states. Similarly, the use of a sedative-hypnotic as premedication prior to surgery or some unpleasant medical procedure is rational and proper (Table 22—2). If the patient presents with chronic anxiety as the primary complaint, it may be appropriate to review the diagnostic criteria set forth in the *Diagnostic & Statistical Manual of Mental Disorders (DSM IV)* to determine whether the diagnosis is correct and if treatment should include drug therapy. For example, excessive or unreasonable anxiety about life circumstances (generalized anxiety disorder), panic disorders, and agoraphobia are amenable to drug therapy, usually in conjunction with psychotherapy. In some cases, anxiety may be a symptom of other psychiatric problems that may warrant the use of pharmacologic agents such as antidepressant or antipsychotic drugs.

The benzodiazepines continue to be the drugs most commonly used for management of anxiety states, including generalized anxiety disorder. Since anxiety symptoms may be relieved by many benzodiazepines, it is not always easy to demonstrate the superiority of one drug over another. However, alprazolam is particularly effective in the treatment of panic disorders and agoraphobia and is more selective in this regard than other benzodiazepines. Alprazolam is also reported to have efficacy similar to that of tricyclic antidepressants in major depressive disorders. The choice of benzodiazepines for anxiety is based on several sound pharmacologic principles: (1) a relatively high therapeutic index (see drug B in Figure 22–1), plus availability of flumazenil for treatment of overdose; (2) a low risk of drug interactions based on liver enzyme induction; (3) slow elimination rates, which may favor persistence of useful central nervous system effects; and (4) a low risk of physiologic dependence, with minor withdrawal symptoms.

Disadvantages of the benzodiazepines include the tendency to develop psychologic dependence, the formation of active metabolites, amnesic effects, and their higher cost. In addition, the benzodiazepines exert additive central nervous system depression when admin-

Table 22–2. Clinical uses of sedative-hypnotics.

For relief of anxiety

For insomnia

For sedation and amnesia before medical and surgical procedures

For treatment of epilepsy and seizure states

As a component of balanced anesthesia (intravenous administration)

For control of ethanol or other sedative-hypnotic withdrawal states

For muscle relaxation in specific neuromuscular disorders

As diagnostic aids or for treatment in psychiatry

istered with other drugs, including ethanol. The patient should be warned of this possibility to avoid impairment of performance of any task requiring mental alertness and motor coordination. Many of the disadvantages of benzodiazepines are not shared by buspirone, which appears to be the most selective anxiolytic of the currently available drugs. However, limitations of buspirone include the extremely slow onset of its anxiolytic actions—confining its use to generalized anxiety—and its limited efficacy in anxiety states that feature panic attacks and phobic characteristics.

Perhaps the most important guide to anxiolytic therapy is the recommendation to use the drug selected with appropriate restraint so as to minimize adverse effects. A dose should be prescribed that does not impair mentation or motor functions during working hours. Some patients may tolerate the drug better if most of the daily dose is given at bedtime, with smaller doses during the day. Prescriptions should be written for short periods, since there is little justification for long-term therapy. The physician should make an effort to assess the efficacy of therapy from the patient's subjective responses. Combinations of antianxiety agents should be avoided, and people taking sedatives should be cautioned about the consumption of alcohol and the concurrent use of over-the-counter medications containing antihistaminic or anticholinergic drugs (see Chapter 64).

Phenobarbital, meprobamate, and sedative-autonomic drugs are used occasionally as antianxiety agents. For example, the antihistaminics (diphenhydramine, hydroxyzine, promethazine) continue to be used presurgically for their sedative and muscarinic receptor blocking actions.

Beta-blocking drugs (eg, propranolol) may be used as antianxiety agents in situations such as performance anxiety. The sympathetic nervous system overactivity associated with anxiety appears to be satisfactorily relieved by the β-blockers, and a slight improvement in the nonsomatic components of anxiety may also occur. Adverse central nervous system effects of propranolol include lethargy, vivid dreams, and hallucinations.

The antihypertensive drug clonidine has usefulness in suppressing anxiety in the management of withdrawal from dependence on nicotine or opioid analgesics. Concomitant treatment with drugs that exert α-adrenoceptor-blocking actions (including tricyclic antidepressants) may decrease the effects of clonidine. Withdrawal from clonidine after protracted use, especially at high doses, has led to life-threatening hypertensive crisis (see Chapter 11).

TREATMENT OF SLEEP PROBLEMS

The complaint of insomnia embraces a wide variety of sleep problems that include difficulty in falling asleep, frequent awakenings, short duration of sleep,

and "unrefreshing" sleep. Insomnia is a serious complaint calling for careful evaluation to uncover possible causes (organic, psychologic, situational, etc) that can perhaps be managed without hypnotic drugs. Nonpharmacologic therapies that are sometimes useful include proper diet and exercise, avoiding stimulants before retiring, ensuring a comfortable sleeping place, and retiring at a regular time each night. In some cases, however, the patient will need and should be given a sedative-hypnotic for a limited period. It should be noted that the abrupt discontinuance of most drugs in this class can lead to rebound insomnia.

Claims have sometimes been made for superiority of one sedative-hypnotic over another based on differential actions on sleep architecture. Benzodiazepines can cause a dose-dependent decrease in both REM and slow wave sleep, though to a lesser extent than the barbiturates. Zolpidem appears to be even less likely than the benzodiazepines to change sleep patterns. However, so little is known about the clinical impact of these effects that statements about the desirability of a particular drug based on its effects on sleep architecture have more theoretical than practical significance. Clinical criteria of efficacy in alleviating a particular sleeping problem are more useful. The drug selected should be one that provides sleep of fairly rapid onset (decreased sleep latency) and sufficient duration, with minimal "hangover" effects such as drowsiness, dysphoria, and mental or motor depression the following day. While older drugs such as chloral hydrate, secobarbital, and pentobarbital are still used, benzodiazepines are generally preferred. Daytime sedation is more common with benzodiazepines that have slow elimination rates (eg, lorazepam) and those that are biotransformed to active metabolites (eg, flurazepam, quazepam). If hypnotics are used every night, tolerance can occur, leading to dose increases by the patient to produce the desired effect. It should be recalled that if physiologic dependence develops, the shorter-acting drugs are associated with more intense withdrawal signs when discontinued. These can include rebound anxiety and insomnia, restlessness, tinnitus, increased reflex activity, and possibly seizures. Anterograde amnesia occurs to some degree with all hypnotic benzodiazepines. Zaleplon and zolpidem have efficacies similar to those of the hypnotic benzodiazepines in the management of sleep disorders. Favorable clinical features of zolpidem include modest day-after psychomotor depression with few amnestic effects. Clinical experience with zaleplon is limited. The drug acts rapidly, but—because of its short half-life—it is less likely to maintain a sleep state in patients who awaken prematurely. At recommended doses, zaleplon appears to cause less amnesia or day-after somnolence than zolpidem. To date, the development of tolerance or dependence has not been reported following the use of zaleplon. The

drugs commonly used for sedation and hypnosis are listed in Table 22-3 together with recommended doses. *Note: Long-term use of hypnotics is irrational and dangerous medical practice.*

OTHER THERAPEUTIC USES

Table 22-2 summarizes several other important clinical uses of drugs in the sedative-hypnotic class. Drugs used in the management of seizure disorders and for intravenous anesthesia are discussed in Chapters 24 and 25.

For sedative and possible amnesic effects during medical or surgical procedures such as endoscopy and bronchoscopy—as well as for premedication prior to anesthesia—oral formulations of shorter-acting drugs are preferred. When drug administration is under close supervision, the danger of accidental or intentional overdosage is less than in the outpatient situation, and a barbiturate may be as appropriate as any other sedative-hypnotic.

Long-acting drugs such as chlordiazepoxide and diazepam and, to a lesser extent, phenobarbital are administered in progressively decreasing doses to patients during withdrawal from physiologic dependence on ethanol or other sedative-hypnotics.

Meprobamate and, more recently, the benzodiazepines have frequently been used as central muscle relaxants, though evidence for general efficacy without accompanying sedation is lacking. A possible exception is diazepam, which has useful relaxant effects in skeletal muscle spasticity of central origin (see Chapter 27).

Psychiatric uses of benzodiazepines other than treatment of anxiety states include the initial management of mania, the control of drug-induced hyperexcitability states (eg, phencyclidine intoxication), and possibly the treatment of major depressive disorders with alprazolam. Sedative-hypnotics are also used occasionally as diagnostic aids in neurology and psychiatry.

CLINICAL TOXICOLOGY OF SEDATIVE-HYPNOTICS

Direct Toxic Actions

Many of the common adverse effects of drugs in this class are those resulting from dose-related depression of central nervous system functions. Relatively low doses may lead to drowsiness, impaired judgment, and diminished motor skills, sometimes with a significant impact on driving ability, job performance, and personal relationships. Benzodiazepines may cause a significant dose-related anterograde amnesia; they can significantly impair ability to learn new information, particularly that involving effortful cognitive processes, while leaving the retrieval of previously learned information intact. This effect is utilized to advantage in uncomfortable procedures, eg, endoscopy, since the appropriate dose leaves the patient able to cooperate during the procedure but amnesic regarding it afterward. The criminal use of benzodiazepines in cases of "date rape" is based on their dose-dependent amnestic effects. Hangover effects are not uncommon following use of hypnotic drugs with long elimination half-lives. Because elderly patients are more sensitive to the effects of sedative-hypnotics, doses approximately half of those used in younger adults are safer and usually as effective. The most common reversible cause of confusional states in the elderly is overuse of sedative-hypnotics. At higher doses, toxicity may present as lethargy or a state of exhaustion or, alternatively, in the form of gross symptoms equivalent to those of ethanol intoxication. The titration of useful therapeutic effects against such unwanted effects is usually more difficult with sedative-hypnotics that exhibit steep dose-response relationships of the type shown

Table 22-3. Dosages of drugs used commonly for sedation and hypnosis.

Sedation		Hypnosis	
Drug	Dosage	Drug	Dosage (at Bedtime)
Alprazolam (Xanax)	0.25–0.5 mg 2–3 times daily	Chloral hydrate	500–1000 mg
Buspirone (BuSpar)	5–10 mg 2–3 times daily	Estazolam (ProSom)	0.5–2 mg
Chlordiazepoxide (Librium)	10–20 mg 2–3 times daily	Flurazepam (Dalmane)	15–30 mg
Clorazepate (Tranxene)	5–7.5 mg twice daily	Lorazepam (Ativan)	2–4 mg
Diazepam (Valium)	5 mg twice daily	Quazepam (Doral)	7.5–15 mg
Halazepam (Paxipam)	20–40 mg 3–4 times daily	Secobarbital	100–200 mg
Lorazepam (Ativan)	1–2 mg once or twice daily	Temazepam (Restoril)	10–30 mg
Oxazepam (Serax)	15–30 mg 3–4 times daily	Triazolam (Halcion)	0.125–0.5 mg
Phenobarbital	15–30 mg 2–3 times daily	Zalepon (Sonata)	5–20 mg
Prazepam (Centrax)	10–20 mg 2–3 times daily	Zolpidem (Ambien)	5–10 mg

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in Figure 22–1 (drug A), including the barbiturates, chloral hydrate, and piperidinediones. The physician should be aware of variability among patients in terms of doses causing adverse effects. An increased sensitivity to sedative-hypnotics is more common in patients with cardiovascular disease, respiratory disease, or hepatic impairment and in older patients. Sedative-hypnotics can exacerbate breathing problems in patients with chronic pulmonary disease and in those with symptomatic sleep apnea.

Sedative-hypnotics are the drugs most frequently involved in deliberate overdoses, in part because of their general availability as very commonly prescribed pharmacologic agents. The benzodiazepines are considered to be "safer" drugs in this respect, since they have flatter dose-response curves. Epidemiologic studies on the incidence of drug-related deaths support this general assumption—eg, 0.3 deaths per million tablets of diazepam prescribed versus 11.6 deaths per million capsules of secobarbital in one study. Of course, many factors other than the specific sedative-hypnotic could influence such data—particularly the presence of other central nervous system depressants, including ethanol. In fact, most serious cases of drug overdosage, intentional or accidental, do involve polypharmacy; and when combinations of agents are taken, the practical safety of benzodiazepines may be less than the foregoing would imply.

The lethal dose of any sedative-hypnotic varies with the patient and the circumstances (Chapter 59). If discovery of the ingestion is made early and a conservative treatment regimen is started, the outcome is rarely fatal, even following very high doses. On the other hand, for most sedative-hypnotics—with the exception of benzodiazepines—a dose as low as ten times the hypnotic dose may be fatal if the patient is not discovered or does not seek help in time. With severe toxicity, the respiratory depression from central actions of the drug may be complicated by aspiration of gastric contents in the unattended patient—an even more likely occurrence if ethanol is present. Loss of brain stem vasomotor control, together with direct myocardial depression, further complicates successful resuscitation. In such patients, treatment consists of ensuring a patent airway, with mechanical ventilation if needed, and maintenance of plasma volume, renal output, and cardiac function. Use of a positive inotropic drug such as dopamine, which preserves renal blood flow, is sometimes indicated. Hemodialysis or hemoperfusion may be used to hasten elimination of some of these drugs.

Flumazenil reverses the sedative actions of benzodiazepines. However, its duration of action is short and its antagonism of respiratory depression unpredictable. Therefore, the use of flumazenil in benzodiazepine overdose *must* be accompanied by adequate monitoring and support of respiratory function.

The extensive clinical use of triazolam has led to reports of serious central nervous system effects in-cluding behavioral disinhibition, delirium, aggression, and violence. While behavioral disinhibition may occur with sedative-hypnotic drugs, it does not appear to be more prevalent with triazolam than with other benzodiazepines. Disinhibitory reactions during benzodiazepine treatment are more clearly associated with the use of very high doses and the pretreatment level of patient hostility.

Adverse effects of the sedative-hypnotics that are not referable to their CNS actions occur infrequently. Hypersensitivity reactions, including skin rashes, occur only occasionally with most drugs of this class. Reports of teratogenicity leading to fetal deformation following use of piperidinediones and certain benzodiazepines justify caution in the use of these drugs during pregnancy. Because barbiturates enhance porphyrin synthesis, they are absolutely contraindicated in patients with a history of acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, or symptomatic porphyria.

Alterations in Drug Response

Depending on the dosage and the duration of use, tolerance occurs in varying degrees to many of the pharmacologic effects of sedative-hypnotics. This can be demonstrated experimentally during chronic use in humans by changes in the effects of these drugs on the electroencephalogram and other characteristics of the stages of sleep. Clearly, tolerance must occur with respect to other effects, since it is known that chronic abusers sometimes ingest quantities of sedative-hypnotics many times the conventional dosage without experiencing severe toxicity. However, it should not be assumed that the degree of tolerance achieved is identical for all pharmacologic effects; there is evidence that the lethal dose range is not altered significantly by the chronic use of sedative-hypnotics. Cross-tolerance between the different sedative-hypnotics, including ethanol, can lead to an unsatisfactory therapeutic response when standard doses of a drug are used in a patient with a recent history of excessive use of these agents. Molecular mechanisms underlying tolerance development in the case of the benzodiazepines may involve changes in GABA$_A$-benzodiazepine receptors. Decreases in brain benzodiazepine receptor densities, measured with single photon emission computed tomography (SPECT), occur during chronic benzodiazepine administration in humans.

With the chronic use of sedative-hypnotics, especially if doses are increased, a state of physiologic dependence can occur. This may develop to a degree unparalleled by any other drug group, *including the opioids*. Withdrawal from a sedative-hypnotic can have severe and life-threatening manifestations. Withdrawal symptoms range from restlessness, anxiety, weakness, and orthostatic hypotension to hyperactive reflexes and generalized seizures. The severity of withdrawal symptoms depends to a large extent on the dosage range used immediately prior to discon-

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tinuance but also on the particular drug. For example,
barbiturates such as secobarbital or pentobarbital in a
dosage of less than 400 mg/d, or diazepam in a
dosage of less than 40 mg/d, may produce only mild
symptoms of withdrawal when discontinued. On the
other hand, the use of more than 800 mg/d of barbi-
turates or 50–60 mg/d of diazepam for 60–90 days
is likely to result in seizures if abrupt withdrawal
is attempted. Symptoms of withdrawal are usually
more severe following discontinuance of sedative-
hypnotics with shorter half-lives. Symptoms are less
pronounced with longer-acting drugs. which may
partly accomplish their own "tapered" withdrawal by
virtue of their slow elimination. Cross-dependence,
defined as the ability of one drug to suppress absti-
nence symptoms from discontinuance of another
drug. is quite marked among sedative-hypnotics. This
provides the rationale for therapeutic regimens in the
management of withdrawal states: Longer-acting
drugs such as chlordiazepoxide, diazepam, and phe-
nobarbital can be used to alleviate withdrawal symp-
toms of shorter-acting drugs, including ethanol.

Drug Interactions

The most frequent drug interactions involving
sedative-hypnotics are interactions with other central

nervous system depressant drugs, leading to additive
effects. These interactions have some therapeutic
utility with respect to the use of these drugs as pre-
medicants or anesthetic adjuvants. However, if not
anticipated, they can lead to serious consequences.
including enhanced depression with concomitant use
of many other drugs. Additive effects can be pre-
dicted with concomitant use of alcoholic beverages,
opioid analgesics, anticonvulsants, and phenothi-
azines. Less obvious but just as important is en-
hanced central nervous system depression with a va-
riety of antihistamines, antihypertensive agents, and
antidepressant drugs of the tricyclic class.

Interactions involving changes in the activity of
hepatic drug-metabolizing enzyme systems can oc-
cur, especially following continuous use of barbitu-
rates or meprobamate. For example, in humans, bar-
biturates have been shown to increase the rate of
metabolism of dicumarol, phenytoin, digitalis com-
pounds, and griseofulvin—effects that could lead to
decreased response to these agents. This type of drug
interaction has not been reported following continu-
ous use of benzodiazepines. Cimetidine, which is
known to inhibit hepatic metabolism of many drugs.
doubles the elimination half-life of diazepam, pre-
sumably via inhibition of its metabolism.

PREPARATIONS AVAILABLE

Benzodiazepines
 Alprazolam (Xanax)
  Oral: 0.25. 0.5, 1, 2 mg tablets
 Chlordiazepoxide (generic, Librium, others)
  Oral: 5, 10, 25 mg tablets, capsules
  Parenteral: 100 mg powder for injection
 Clorazepate (generic. Tranxene)
  Oral: 3.75, 7.5, 15 mg tablets and capsules
  Oral sustained-release: 11.25, 22.5 mg tablets
 Clonazepam (Klonopin)
  Oral: 0.5, 1, 2 mg tablets
 Diazepam (generic, Valium, others)
  Oral: 2, 5, 10 mg tablets; 5 mg/5 mL. 5 mg/mL
   solutions
  Oral sustained-release: 15 mg capsules
  Parenteral: 5 mg/mL for injection
 Estazolam (ProSom)
  Oral: 1, 2 mg tablets
 Flurazepam (generic, Dalmane)
  Oral: 15, 30 mg capsules
 Halazepam (Paxipam)
  Oral: 20, 40 mg tablets
 Lorazepam (generic, Ativan, Alzapam)
  Oral: 0.5, 1, 2 mg tablets
  Parenteral: 2, 4 mg/mL for injection
 Midazolam (Versed)
  Parenteral: 1, 5 mg/mL in 1, 2, 5, 10 mL, vials
   for injection

 Oxazepam (generic. Serax)
  Oral: 10, 15, 30 mg capsules, 15 mg tablets
 Prazepam (Centrax)
  Oral: 5, 10, 20 mg capsules, 10 mg tablets
 Quazepam (Doral)
  Oral: 7.5, 15 mg tablets
 Temazepam (generic. Restoril)
  Oral: 15, 30 mg capsules
 Triazolam (Halcion)
  Oral: 0.125, 0.25 mg tablets

Benzodiazepine Antagonist
 Flumazenil (Romazicon)
  Parenteral: 0.1 mg/mL. for IV injection

Barbiturates
 Amobarbital (Amytal)
  Parenteral: powder in 250, 500 mg vials to re-
   constitute for injection
 Aprobarbital (Alurate)
  Oral: 40 mg/5 mL elixir
 Butabarbital sodium (generic, Butisol, others)
  Oral: 15, 30, 50, 100 mg tablets; 30 mg/5 mL
   elixirs
 Mephobarbital (Mebaral)
  Oral: 32, 50, 100 mg tablets

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Pentobarbital (generic, Nembutal Sodium)
Oral: 50, 100 mg capsules
Rectal: 30, 60, 120, 200 mg suppositories
Parenteral: 50 mg/mL for injection
Phenobarbital (generic, Luminal Sodium, others)
Oral: 15, 16, 30, 60, 100 mg tablets; 16 mg
capsules; 15, 20 mg/5 mL elixirs
Parenteral: 30, 60, 65, 130 mg/mL for injection
Secobarbital (generic, Seconal)
Oral: 100 mg capsules
Parenteral: 50 mg/mL for injection

Miscellaneous Drugs
Buspirone (BuSpar)
Oral: 5, 10 mg tablets
Chloral hydrate (generic, Noctec, Aquachloral
Supprettes)
Oral: 250, 500 mg capsules; 250. 500 mg/5 mL
syrups
Rectal: 324, 500, 648 mg suppositories

Ethchlorvynol (Placidyl)
Oral: 200, 500, 750 mg capsules
Ethinamate (Valmid Pulvules)
Oral: 500 mg capsules
Hydroxyzine (generic, Atarax, Vistaril)
Oral: 10, 25, 50, 100 mg tablets; 25, 50, 100
mg capsules; 10 mg/5 mL syrup; 25 mg/5
mL suspension
Parenteral: 25, 50 mg/mL for injection
Meprobamate (generic, Miltown, Equanil, others)
Oral: 200, 400, 600 mg tablets
Oral sustained-release: 200, 400 mg capsules
Paraldehyde (generic)
Oral, rectal liquids
Zaleplon (Sonata)
Oral: 5, 10 mg capsules
Zolpidem (Ambien)
Oral: 5. 10 mg tablets

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